PROFILE OF PRIMARY MEMBRANOUS NEPHROPATHY AMONG MEMBRANOUS NEPHROPATHY PATIENTS BASED ON PLA2 RECEPTOR STAINING IN BIOPSY

DISSERTATION SUBMITTED TO THE TAMILNADU

DR.M.G.R. MEDICAL UNIVERSITY, CHENNAI

In partial fulfilment of the requirements for the degree of

M.D. BRANCH – I

(GENERAL MEDICINE)

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DEPARTMENT OF GENERAL MEDICINE

TIRUNELVELI MEDICAL COLLEGE HOSPITAL

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MAY-2021

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DECLARATION

I solemnly declare that the dissertation entitled "**PROFILE OF PRIMARY MEMBRANOUS NEPHROPATHY AMONG MEMBRANOUS NEPHROPATHY PATIENTS BASED ON PLA2 RECEPTOR STAINING IN BIOPSY "** is done by me at Tirunelveli Medical College Hospital, Tirunelveli Under the guidance and supervision of **Prof.Dr.Ravichandran M.D.,** the dissertation is submitted to The Tamilnadu Dr. M.G.R. Medical University towards the partial fulfilment of requirements for the award of M.D. Degree (Branch I) in General Medicine.

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PROTOCOL TITLE: PROFILE OF PRIMARY MEMBRANOUS NEPHROPATHY AMONG MEMBRANOUS NEPHROPATHY PATIENTS BASED ON PLA2 RECEPTOR STAINING IN BIOPSY.
PRINCIPAL INVESTIGATOR: DR.V.S.MOHAMED AASEEM ARSHAD, MBBS,
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Dear Dr.V.S.MOHAMED AASEEM ARSHAD, MBBS., The Tirunelveli Medical College Institutional Ethics Committee (TIREC) reviewed and discussed your application during The IEC meeting held on 30.11.2018.

THE FOLLOWING DOCUMENTS WERE REVIEWED AND APPROVED

1.	TIREC Application Form	☐
2.	Study Protocol	☐
3.	Department Research Committee Approval	☐
4.	Patient Information Document and Consent Form in English and Vernacular Language	☐
5.	Investigator's Brochure	☐
6.	Proposed Methods for Patient Accrual Proposed	☐
7.	Curriculum Vitae of The Principal Investigator	☐
8.	Insurance /Compensation Policy	☐
9.	Investigator's Agreement with Sponsor	☐
10.	Investigator's Undertaking	☐
11.	DCGI/DGFT approval	☐
12.	Clinical Trial Agreement (CTA)	☐
13.	Memorandum of Understanding (MOU)/Material Transfer Agreement (MTA)	☐
14.	Clinical Trials Registry-India (CTRI) Registration	☐

THE PROTOCOL IS APPROVED IN ITS PRESENTED FORM ON THE FOLLOWING CONDITIONS

1. The approval is valid for a period of 2 year/s or duration of project whichever is later
2. The date of commencement of study should be informed
3. A written request should be submitted 3weeks before for renewal / extension of the validity
4. An annual status report should be submitted.
5. The TIREC will monitor the study
6. At the time of PI's retirement/leaving the institute, the study responsibility should be transferred to a person cleared by HOD
7. The PI should report to TIREC within 7 days of the occurrence of the SAE. If the SAE is Death, the Bioethics Cell should receive the SAE reporting form within 24 hours of the occurrence.
8. In the events of any protocol amendments, TIREC must be informed and the amendments should be highlighted in clear terms as follows:
   a. The exact alteration/amendment should be specified and indicated where the amendment occurred in the original project. (Page no. Clause no. etc.)
   b. The PI must comment how proposed amendment will affect the ongoing trial. Alteration in the budgetary status, staff requirement should be clearly indicated and the revised budget form should be submitted.
   c. If the amendments require a change in the consent form, the copy of revised Consent Form should be submitted to Ethics Committee for approval. If the amendment demands a re-look at the toxicity or side effects to patients, the same should be documented.
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   e. Approval for amendment changes must be obtained prior to implementation of changes.
   f. The amendment is unlikely to be approved by the IEC unless all the above information is provided.
   g. Any deviation/violation/waiver in the protocol must be informed..

STANDS APPROVED UNDER SEAL

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CERTIFICATE – II

This is to certify that this dissertation work entitled entitled "**PROFILE OF PRIMARY MEMBRANOUS NEPHROPATHY AMONG MEMBRANOUS NEPHROPATHY PATIENTS BASED ON PLA2 RECEPTOR STAINING IN BIOPSY "** of the candidate **Dr.MOHAMED AASEEM ARSHAD V.S** with registration Number **201811364** for the award of **M.D.** Degree in the branch of **GENERAL MEDICINE (I).** I personally verified the urkund.com website for the purpose of plagiarism check. I found that the uploaded thesis file contains from introduction to conclusion page and result shows 22 **Percentage** of plagiarism in the dissertation.

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CONTENT

LIST OF ABBREVIATION

1.	MN	-	Membranous Nephropathy
2.	IMN	-	Idiopathic Membranous Nephropathy
3.	MPGN	-	Membrano Proliferative Glomerulonephritis
4.	FSGS	-	Focal Segmental Glomerulosclerosis
5.	SLE	-	Systemic Lupus Erythematosis
6.	AKI	-	Acute Kidney Injury
7.	CKD	-	Chronic Kidney Disease
8.	MPR	-	Modified Ponticelli Regimen
9.	PLA2R	-	Phospholipase A2 receptor
10.	NS	-	Nephrotic Syndrome.
11.	BUN	-	Blood Urea Nitrogen

INTRODUCTION

Nephrotic syndrome which was once a primary childhood disease has now evolved and became prevalent in adult population. Even in the nephrology department of Tirunelveli medical college hospital In an average three cases are admitted per week. But on the contrary to paediatric population of the syndrome which is occupied in majority by minimal change disease, the pathogenesis is completely different in adult population .

Primary Diseases	Approximate Incidence in Adults (% of Primary Disease)	Approximate Incidence in Adults (% of All Diseases That Cause Nephrotic Syndrome)
Minimal change disease	10	6
Focal segmental glomerulonephritis	35	21
Membranous nephropathy	30	18
Membranoproliferative glomerulonephritis	5	3
Other	20	12

From the above data , we can see membranous Nephropathy [MN] is one of the leading cause of nephrotic syndrome in the adults . It is characterised by immune deposit formation along the glomerular basement membrane [GBM]. Membranous Nephropathy can be primary or it can be secondary to any underlying diseases which are listed below:

Table 6.10 Major causes of membranous nephropathy

Malignancies	Lung, colon, breast cancer
	Haematological less often
Autoimmune disease	SLE
	Rheumatoid arthritis
Drugs	Penicillamine, gold
	NSAIDs
Infections	Hepatitis B, hepatitis C
	Malaria, schistosomiasis, syphilis
Miscellaneous	Chronic renal transplant rejection
	Sarcoidosis
	Other glomerular diseases

Primary also called as idiopathic membranous Nephropathy is however is common occurring in 60 percent of the cases. It is an antibody mediated autoimmune glomerular disease but the target antigen was unknown since its recognition as a distinct clinicopathologic entity ie 1957. But in 2009, there was

the ground breaking discovery of circulating antibodies to M-type phospholipase A2 receptor present in the podocytes of glomerular filter membrane. Nowadays, the identification of target antigen ie PLA2R using immunoflorescence technique in renal biopsy specimens help in direct identification of idiopathic membranous Nephropathy cases.

Before it's discovery it was a tedious job to rule out all the secondary causes of membranous nephropathy because immunosupression is the treatment option for idiopathic membranous nephropathy while the secondary form usually resolves when the underlying cause is identified and treated.

AIM OF THE STUDY

1. To find the proportion of membranous Nephropathy among adult nephrotic syndrome cases admitted in TVMCH.
2. Sensitivity and specificity of the PLA2R antigen in identifying the idiopathic membranous Nephropathy cases.
3. Clinical, biochemical & histopathological profile of idiopathic membranous Nephropathy (IMN)
4. To study the response of IMN patients to treatment with modified Ponticelli regimen over a period of 6 months.

REVIEW OF LITERATURE

Glomerular diseases may be categorized into those that involve the kidney (primary glomerular diseases) and those in which kidney involvement is part of a systemic disorder (secondary glomerular diseases). . Some forms of glomerular disease occur not only as renal-limited (primary) disease in some patients but also as a part of systemic disease like anti–glomerular basement membrane (anti-GBM) glomerulonephritis with or without pulmonary disease, and ANCA glomerulonephritis with or without systemic vasculitis and granulomatosis. The separation of glomerular disease into primary versus secondary is problematic because, in some instances, primary glomerular diseases are similar, if not identical, to secondary glomerular diseases. For example, immunoglobulin A (IgA) nephropathy, pauci-immune necrotizing and crescentic glomerulonephritis, anti-GBM glomerulonephritis, MN, and membranoproliferative glomerulonephritis (MPGN) can occur as primary kidney diseases or as components of systemic diseases such as IgA vasculitis, pauci-immune small vessel vasculitis, Goodpasture's syndrome, systemic lupus erythematosus (SLE), and cryoglobulinemic vasculitis, respectively. Of note, , as in many settings, to phase out the nosologic use of eponyms and to substitute non-eponymous terms that more accurately reflect pathophysiologic specificity in the nomenclature of vasculitides. This nomenclature of vasculitides was revised in 2012 at second international Chapel Hill Consensus Conference, and the following vasculitides

with new names are relevant : IgA vasculitis (formerly designated Henoch-Schönlein purpura), granulomatosis with polyangiitis (GPA, formerly Wegener's granulomatosis), and eosinophilic granulomatosis with polyangiitis (EGPA, formerly Churg-Strauss syndrome).

When a patient comes with glomerular disease, the physician must not only evaluate the signs and symptoms but also look for evidence of a systemic process or disease that could be causing the renal disease. Clinical evaluation includes assessment of proteinuria, hematuria, the presence or absence of renal failure, and the hypertension. Some glomerular diseases cause isolated proteinuria or hematuria with out any other signs or symptoms of disease. Severe glomerular disease often results in the nephrotic syndrome or nephritic syndrome. Glomerular diseases may have a silent course or begin suddenly, leading to acute or rapidly progressive glomerulonephritis [RPGN] . Although some glomerular diseases consistently cause a specific syndrome (e.g., minimal change disease [MCD] results in the nephrotic syndrome), most diseases are capable of causing features of both nephrotic and nephritic syndrome. This variability of clinical manifestations among the different glomerular diseases will not permit an accurate diagnosis based on clinical features alone. Therefore, renal biopsy has an important role in the evaluation of patients and it remains the gold standard for definitive diagnosis of many glomerular disorders.

Manifestations of Nephrotic and Nephritic Features by Glomerular Diseases		
	Nephrotic Features	Nephritic Features
Minimal change disease	++++	NIL
Membranous nephropathy	++++	+
Focal segmental glomerulosclerosis	+++	++
Fibrillary glomerulonephritis	+++	++
Mesangioproliferative glomerulopathy	++	++
Membranoproliferative glomerulonephritis	++	+++
Proliferative glomerulonephritis	++	+++
Acute diffuse proliferative Glomerulonephritis	+	++++
Crescentic glomerulonephritis	+	++++

NEPHROTIC SYNDROME

Characterized by albuminuria (>3.5 g/d) and hypoalbuminemia (<30 g/L)and accompanied by edema, hyperlipidemia, and lipiduria. Protein excretion could be quantified by 24-hour urine collection or by measurement of the urine protein:creatinine ratio or albumin:creatinine ratio on a random spot urine analysis . The measurement of creatinine excretion helps to define the adequacy of 24-hour urine collections: daily creatinine excretion should be 20–25 milligram/kg in men and 15–20 milligram/kg in women. For random urine samples, the ratio of protein or albumin to creatinine in milligram/dL approx.

nearly the 24-hour urinary protein excretion, since creatinine excretion is only slightly greater than 1000 milligram/day / 1.73 m2. A urine protein:creatinine ratio of 5 is consistent with 5 g/d /1.73 m2. Quantification of urine protein excretion on spot urine has overcome formal 24-hour urine collections, due to the greater ease and the need to verify a complete 24-hour collection. The total protein:creatinine ratio does not detect microalbuminuria, a level of albumin excretion that is below the level of detection by tests for total protein; urine albumin: creatinine measurement is preferred as a good screening tool for mild proteinuria.

In addition to edema, the complications of nephrotic syndrome include renal vein thrombosis and other thromboembolic events, infections, vitamin D deficiency, protein malnutrition, and drug toxicity due to decreased protein binding.

In adults, the most common cause of nephrotic syndrome is diabetes. A minority of cases

are secondary to SLE, amyloidosis, drugs, malignancy , or other disorders . By exclusion, the remaining are idiopathic. With the exception of diabetic nephropathy, a kidney biopsy is required to make the diagnosis and determine therapy in nephrotic syndrome .

Minimal Change Disease

Causes about 10–15% of idiopathic nephrotic syndrome in adults, but 70–90% of nephrotic syndrome in children. BP is normal; GFR is normal or slightly decreased ; urinary sediment is benign or shows few RBCs. Protein selectivity is variable in adults. Recent URI , allergies, or immunizations are present in some of the cases; NSAIDS can cause minimal change disease [MCD] with interstitial nephritis. Acute renal failure may occur, particularly among elderly persons. Kidney biopsy shows only foot process fusion on electron microscopy. Remission of proteinuria with steroids carry a good prognosis; cytotoxic therapy may be required

for relapse cases . Progression to renal failure is not common. Focal sclerosis has been suspected in cases refractory to glucocorticoid therapy.

Membranous GN

It is characterized by subepithelial IgG deposits; accounts for nearly 30% of idiopathic adult nephrotic syndrome . Patients present with edema and nephrotic range proteinuria. B.P, GFR, and urine sediment are usually normal at the initial presentation. Systemic Hypertension, mild renal failure , and abnormal urinary sediments develop later. Renal vein thrombosis is common, than with any other forms of NS. Underlying diseases like SLE, hepatitis B, and solid tumors and exposure to drugs like high-dose captopril or penicillamine should be sought. The majority of patients with idiopathic membranous GN [IMN] have detectable circulating antibodies to the M-typephospholipase A2 (PLA2R), which is

expressed in glomerular podocytes. Some patients progress to end-stage renal disease (ESRD); however, 20–33% may experience spontaneous remission. Male gender, older age, hypertension, and persistence of proteinuria (>6 g/d) are associated with higher risk of progressive disease. Optimal immunosuppressive therapy is controversial. Steroids alone are ineffective. Cytotoxic agents may promote complete or partial remission in some patients , as may cyclosporine. Anti-CD20 antibody therapy with rituximab has shown considerable promise, consistent with the role for B cells and anti-PLA2R antibodies in the pathophysiology of the disease . Reduction of proteinuria with angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs) is also an important mainstay of therapy.

Focal Glomerulosclerosis (FSGS)

It can be primary or secondary. Primary tends to be more acute, similar to minimal change disease in abruptness of Nephrotic syndrome , but with other features of hypertension, renal failure , and hematuria. Involves fibrosis of portions of (primarily juxtamedullary) glomeruli and is found in nearly 35% of patients with nephrotic syndrome . There are different pathologic subtypes of idiopathic FSGS, with prognostic implications. In particular, "collapsing glomerulopathy" variant has some pathologic similarity to HIV-associated nephropathy (HIVAN); both nephropathies cause rapidly progressive disease.

African Americans are disproportionately affected by FSGS, HIVAN, and other nondiabetic kidney disease, with higher incidence, greater susceptibility (HIVAN), and a much higher risk for developing ESRD. "African-specific" variants in the *APOL1* gene, which encodes apolipoprotein L1 expressed in glomerular podocytes, have been implicated in enhanced genetic risk.

Treatment of primary FSGS typically begins with an extended course of steroids; fewer than half of patients undergo remission. Cyclosporine is an alternative therapy for maintenance of remission and for steroid-resistant patients. As in other glomerulopathies, reduction of proteinuria with ACE inhibitors and/or ARBs is also an important component of therapy. Finally, primary FSGS may recur after renal transplant, when it can lead to loss of the allograft.

Secondary FSGS can occur in the late stages of any form of kidney disease associated with nephron loss (e.g., remote GN, pyelonephritis, sickle cell disease, or vesicoureteral reflux). Treatment includes anti-proteinuric therapy with ACE inhibition and BP control. There is no benefit of steroids in secondary FSGS. Clinical history, renal size, biopsy findings, and associated conditions allow the differentiation of primary versus secondary causes.

Membranoproliferative Glomerulonephritis (MPGN)

Mesangial expansion and proliferation extend into the capillary loops. Two ultrastructural variants do exist. In MPGN type I, subendothelial electron-dense deposits are present, C3 is deposited in a granular pattern indicative of immune-complex pathogenesis, and IgG and early components of complement may or may not be present. In MPGN type II, the lamina densa of the GBM is transformed into an electron dense character, as is the basement membrane in Bowman's capsule and tubules. Complement C3 is found irregularly in the Glomerular BM. Small amounts of Immunoglobulins (usually IgM) are present, but early components of complement are absent. Serum complement levels are decreased. MPGN affects young adults. BP and GFR are abnormal, and the urine sediment is active. Some patients have acute nephritis or hematuria. Similar lesions occur in SLE and haemolytic uremic syndrome [HUS]. Infection with hepatitis-C virus (HCV) has been linked to MPGN, often with associated cryoglobulinemia. Treatment with interferon α [INF alfa] and ribavirin has resulted in remission of kidney disease in some cases, depending on HCV serotype; however, renal failure precludes ribavirin therapy. Steroidss , cytotoxic agents, antiplatelets, and plasmapheresis have been used with limited success only; rituximab is a newer therapy with greater evidence of efficacy. MPGN may recur in allografts.

Diabetic Nephropathy

The most common cause of Nephrotic Syndrome . Although duration of diabetes mellitus (DM) is variable, in type- 1 DM proteinuria may develop 10–15 years after the onset of diabetes, progress to nephrotic syndrome , and then leads to renal failure over 3–5 years. Retinopathy is nearly universal in type 1 diabetes patients with nephropathy, such that the absence of retinopathy should prompt consideration of another glomerular lesion (e.g., membranous nephropathy). In contrast, only nearly 60% of type 2 diabetes patients with diabetic nephropathy have retinopathy. Clinical features include proteinuria, progressive hypertension, and progressive renal failure . Pathologic changes include mesangial sclerosis, diffuse, or nodular (Kimmelstiel - Wilson) glomerulosclerosis. However, patients rarely undergo kidney biopsy; yearly measurement of microalbuminuria is routine management for all diabetes patients , the natural history is an important component of diagnosis. Patients typically demonstrate progression from microalbuminuria (30–300 milligram/24 h) to dipstick positive proteinuria (>300 milligram albuminuria) and then progressively overt proteinuria and CKD. However, proteinuria can be variable in diabetic nephropathy, with as much as 25 g/24 hour in the absence of profound renal failure or alternatively with progressive renal failure and stable, modest proteinuria. Treatment with ACE inhibitors delays the onset of nephropathy and ESRD in type 1 diabetes patients with microalbuminuria or declining kidney function and should be instituted in

all patients tolerant to that class of drug. If a cough develops in a patient treated with ACE inhibitor, an ARB is the next choice. Type 2 diabetes with microalbuminuria or proteinuria can be treated with ACE inhibitors or ARBs. Although long term studies are lacking, many authorities suggest combining inhibitors of the renin-angiotensin-aldosterone system , i.e., ARBs, ACE inhibitors, mineralocorticoid receptor blockers like spironolactone , and/or renin inhibitors like aliskiren , in patients with persistent, significant proteinuria. Hyperkalemia, hypotension, or worsening GFR can limit single or combined therapy with RAAS inhibitors. If hyperkalemia develops and cannot be controlled with (1) optimizing glucose control, (2) loop diuretics like frusemide (if otherwise appropriate), or (3) treatment of metabolic acidosis (if present), then tight control of BP with

alternative agents is required .

EVALUATION OF NEPHROTIC SYNDROME
Random spot urine for protein and creatinine Serum albumin, cholesterol, complement Urine protein electrophoresis Rule out SLE, diabetes mellitus Review drug exposure Renal biopsy Consider malignancy (in elderly pt with membranous GN or minimal change disease) Consider renal vein thrombosis (if membranous GN or symptoms of pulmonary embolism are present)

MEMBRANOUS NEPHROPATHY

EPIDEMIOLOGY

Membranous nephropathy (MN), is one in all the foremost common causes of nephrotic syndrome in adults. MN occurs as a primary glomerular disease caused by antibodies specific for M-type phospholipase A2 receptor (PLA2R) or secondary to multiple systemic diseases, like autoimmune diseases (SLE, autoimmune thyroiditis), infections (hepatitis- B, hepatitis- C, malaria), drugs (penicillamine, gold etc.), and malignancies (colon , breast or lung cancer). Secondary MN, is more frequent in children than in

adults. In patients older than 60, MN is related to malignancy in 20% to 30% of cases. MN is that the explanation for nephrotic syndrome in nearly 25% of adults. A study of cases who had urinary excretion of over 1 gram of protein per 24 hours, conducted by the Medical Research Council [MRC] within the U.K from 1978 to 1990, determined that 20% of patients had MN. the height incidence of MN is within the 4th to 5th decade of life. A pooled analysis of studies of patients with idiopathic Membranous Nephropathy found a 2 : 1 predominance of males than females . The adult/child ratio was 26 : 1 (1734 adults and 67 children); though most patients with MN present with nephrotic syndrome, 10% to twenty of patients have proteinuria that is still less than 2 grams of protein per day. it's likely that the frequency of MN within the general population is underestimated, because asymptomatic patients with subclinical proteinuria often don't come to diagnosis or undergo renal biopsy.

The association of MN with underlying malignancy is well recognized. in an exceedingly large cohort study of 240 patients , the incidence of cancer was significantly higher in patients with MN than within the general population (standardized incidence ratio, 9.8 for men and 12.3 [4.5 to 26.9] for women). In nearly 1/2 the patients, the tumor was asymptomatic and was detected only thanks to diagnostic procedures prompted by the diagnosis of MN. the foremost common malignancies were cancers of the lung , prostate and breast . Risk factors for cancer in patients with MN include adulthood and history of smoking, although the clinical presentation doesn't vary between patients with cancer associated

MN and people with primary MN. In patients with cancer-associated MN, treatment of the cancer is related to a reduction of proteinuria. These studies show the importance of cancer screening among older patients with MN, not only at the time of initial diagnosis but also during subsequent long-term follow-up.

CLINICAL FEATURES AND EXPLANATION

Patients with membranous nephropathy can be asymptoamtic or the pateints may present with symptoms like facial puffines, abdominal distention and pedal edema .The patient may also have anemia , hematuria is very rare . The most common renal syndromes are as follows:

1.nephritic syndrome

2.nephrotic syndrome

3.acute renal failure

4.chronic renal failure

5.nephrolithiasis

6.obstructive uropathy

7.systemic hypertension

8.renovascular disease

Out of these , membranous nephropathy presents with nephrotic syndrome though few people may have subclinical proteinuria . The facial puffiness is mostly early morning and it is due to loose areolar tissue around the eyelid.Facial puffiness occurring prior to ascites and pedal edema is specific for renal disease .In hepatobiliary disease , volume overload begins with ascites because the

pathogenesis is portal hypertension . In cardiac failure the edema is mainly dependent edema occurring first in ankle in ambulatory patients.The mechanism of ascites in nephrotic syndrome is hypoalbuminemia because albumin synthesised by the liver is excreted in excess by the kidneys . The other mechanisms responsible for ascites like arterial underflow and venous overflow play only a minor role in nephrotic syndrome Patients with MN usually have syndrome with 1. hypoalbuminemia, 2.hyperlipidemia , 3. peripheral edema,4.lipiduria.Hyperlipidemia is due to an over active liver which synthesises for apolipoproteins and albumin to compensate the excess loss via the urine.

The different types of proteinuria are :

1.selective proteinuria

2.non selective proteinuria

3.glomerular proteinuria

4.tubular proteinuria

5.orthostatic proteinuria

6.transient proteinuria.

The proteinuria in membranous nephropathy is non selective and glomerular . As it is non selective there is excretion of not only albumin but also other serum proteins like thyroglobulins , apoferritin , ceruloplasmin , globulin , fibrinogen, protein c , protein and antithrombin 3 . Decrease in thyroglobulin leads to hypothyroidism, apoferritin deficiency causes anemia , ceruloplasmin deficiency causes impairment in copper transport , thrombosis due to protein c , protein s and antithrombin 3 deficiency .There

are reports of young females with membranous nephropathy presenting with cortical vein thrombosis .

Hypertension could also be present at the outset of disease in 13% to 55% of patients. The reason for hypertension in these patients are :

1.Salt and water retention due to secondary hyperaldosteronism

2.Increased ECF volume

Hence treatment of hypertension is through the following means :

1.Salt restriction [less than 2 grams of sodium]

2.fluid restriction as dictated by the volume status of the patient.

3Anti hypertensives like ACE inhibitors or ARBs , spironolactone which combats the secondary hyperaldosteronism. But careful monitoring of serum potassium levels and renal function is essential . A rise in creatinine of upto thirty percent is acceptable after starting ACE inhibitors or ARBs.

Most patients present with normal or slightly decreased kidney function at presentation. If progressive renal disorder develops, it's usually relatively mild. An abrupt change to more acute kidney disease should prompt investigation of a superimposed condition, like a crescentic glomerulonephritis. One third of those patients have anti-GBM antibodies, have ANCAs. Other causes of sudden deterioration of kidney function include acute bilateral vein thrombosis, and hypovolemia , hypotension within the setting of massive nephrotic syndrome. The incidence of vena renalis thrombosis in MN varies from 4% to 52%. The diagnosis of vein thrombosis could also be clinically apparent supported the sudden

development of macroscopic hematuria, flank pain, and raised rft values, but a more gradual development is additionally common. Although ultrasonography with Doppler studies may demonstrate the renal thrombus, venography with contrast remains the investigation of choice.

Drug-induced kidney injury is one more reason for the sudden deterioration in kidney function in a very patient with MN.

NSAIDS can cause :

1.interstitial nephritis

2.Nephrotic syndrome

3.Papillary necrosis

4.Pre renal failure.

Drugs causing interstitial nephritis are many , some of the common being :

1.PPI inhibitors

2.Antibiotics like penicillin

3.Rifampicin

4.Antiepileptics like valproate , levetiracetam and phenytoin

Drugs like gentamycin and amikacin causes acute tubular necrosis. Other drugs like cyclosporine and tacrolimus are also directly nephrotoxic .ACE inhibitors ,ARBs , NSAIDS can lead to sudden worsening of renal failure due to prerenal hemodynamic alterations.

Sepsis and infections can also worsen renal failure in membranous nephropathy patients. MN patients are immunocompromised making them more prone to infections.

An estimate of renal survival in patients with MN is obtained from a pooled analysis of outcomes in clinical studies. during this analysis of 1189 pooled patients, the probability of kidney survival was 86% at 5 years, 65% at 10 years, and 59% at 15 years. Although 35% of patients may get to ESRD by 10 years, 25% may experience an entire spontaneous remission of proteinuria within 5 years. in a very study in Italy of 100 untreated patients with MN who were followed for 10 years, 30% had progressive renal impairment after 8 years of follow-up. On the opposite hand, of the 62% who presented with nephrotic-range proteinuria, 50% underwent spontaneous remission in 5 years.

Persistent proteinuria is more predictive of renal disorder than proteinuria at one time point. Thus, persistent proteinuria of 8 g or more of protein per day for a minimum of 6 months was related to a 66% probability of progressive chronic nephropathy (CKD). Patients with a minimum of 6 g of protein per day for 9 months or longer had a 55% probability of developing CKD. Persistent proteinuria of 4 g or more of protein per day for extended than 18 months was related to a good greater risk of CKD.

In addition to decreased GFR and proteinuria, other factors is also related to an increased risk of progressive kidney failure. Male sex, advanced age (older than age 50), SHT, and reduced GFR at presentation are reported as risk factors for progressive decline in kidney function. The GFR is at a maximum for any individual at the age of 30. Right from thirty years of age , the GFR decreases by one ml/kg/hour for one age

. additionally to the clinical prognostic features, the presence of advanced MN on kidney biopsy specimens (stage III or IV), tubular atrophy, and interstitial fibrosis can even be related to increased risk. In fact, interstitial fibrosis and tubular atrophy are shown to be independent predictors of progressive failure in primary MN.The presence of crescents on kidney biopsy specimens may predict a poor long-term prognosis. The stage of glomerular lesions detected by microscopy has also been suggested as a risk factor for poor prognosis in some studies. Similarly, FSGS superimposed on MN may have a worse longterm prognosis than MN without sclerosis. However, the importance of those demographic and histologic risk factors wasn't substantiated in an exceedingly retrospective analysis of an oversized cohort of patients from the University of Toronto . Of the histologic variables, only a greater degree of complement deposition perceived to be related to a more rapid worsening of renal function.

In a prospective study, a urinary excretion of beta2- microglobulin level of over 0.5 microgram/mt and a urinary IgG level of over 250 milligram/24 hr, assessed in a very timed urine sample, were found to predict progressive loss of GFR in an exceedingly prospective cohort of 57 patients with primary MN and normal kidney function. in a very statistical procedure, urine beta2-microglobulin excretion was the strongest independent predictor of the event of nephrotic syndrome, with a sensitivity and specificity of 88% and 91%, respectively. Unfortunately, the measurement of urine beta2-microglobulin is tedious because it's unstable in urine and it requires alkalinisation of the urine before collection. More recently, there are several studies

from different groups demonstrating an association between high anti-PLA2R autoantibodies and worse long-term outcomes i.e an inverse correlation between the extent of the autoantibodies and also the disease.

In summary, one in all the strongest predictor of progressive disease appears to be persistence of moderate proteinuria. Impaired renal function, severe proteinuria at presentation, the presence of considerable interstitial infiltrates on biopsy specimen, superimposed crescentic glomerulonephritis, and FSGS also portend a poorer outcome.

PATHOGENESIS

MN is caused by immune complex localization within the sub-epithelial zone of glomerular capillaries. The nephritogenic antigens may be endogenous to the glomerulus (e.g., podocyte autoantigens) or are often exogenous (e.g., hepatitis B antigens). within the latter case, the antigen could also be deposited within the subepithelial zone as part of preformed, circulating, immune complexes, or may be planted within the subepithelial zone as free antigen to which antibodies bind to make immune complexes in place. In rat Heymann's nephritis, an animal model that very closely resembles human primary MN, there's convincing evidence that the subepithelial immune deposits form in place as a results of the binding of antibodies to glycoproteins produced by podocytes followed by accumulation of masses of the immune complexes within the subepithelial zone.

The long-standing seek for antigens targeted in a very sizable amount of patients with MN has recently witnessed significant breakthroughs. The podocyte neutral

endopeptidase was identified because the endogenous target of autoantibodies in neonate with syndrome. This antibody crossed the placenta and was induced within the mother, who lacked neutral endopeptidase epitope thanks to a mutational deletion. Sensitization to the nascent antigen was induced during a previous pregnancy. Although this target antigen doesn't account for a big proportion of MN cases, these findings provide mission for the idea of in place immune complex formation within the pathogenesis of human primary MN, and constitute an example of alloimmunization resulting in the generation of immune complex–mediated Nephropathy .

The team of Beck and Salant identified M-type PLA2R because the target antigen common for about 70% of patients with primary MN. In contrast, none of the sera from normal controls, patients with MN secondary to SLE or viral hepatitis, patients with conditions aside from MN, or other autoimmune disorders reacted with this antigen. Anti-PLA2R autoantibodies in serum samples from patients with primary MN were predominantly of the IgG4 subclass, which is that the predominant immunoglobulin subclass seen in glomerular deposits of patients with this disease.PLA2R expression in podocytes was confirmed by immunofluorescence microscopy and in cultured human podocytes, indicating that this target antigen is intrinsic to glomeruli instead of deposited from sera of patients with primary MN. Analysis of serial samples from patients with Membranous Nephropathy also suggests a decline or disappearance of anti-PLA2R antibodies with remission of proteinuria.

These findings have been confirmed in additional patients with primary MN by multiple independent groups throughout the planet.

Interestingly, only if only 70% of patients with primary MN harbor autoantibodies to PLA2R, another group identified antibodies to circulating cationic bovine albumen in 11 patients with MN, including 4 children, out of fifty MN patients and 172 controls tested. Bovine albumin was also found to be present in glomerular immune deposits all told four of the kids tested.

In separate studies, the team led by Prunotto detected specific anti–aldose reductase (AR) and anti–manganese enzyme (SOD2) IgG4 in sera of patients with MN. Anti-AR IgG4 and anti-SOD2 IgG4 were also eluted from microdissected glomeruli of patients with MN but not from biopsy specimens of patients with lupus nephritis or MPGN. Anti-AR and anti-SOD2 co-localized with IgG4 and C5b-9 in electron-dense immune deposits. Interestingly, these antigens were detected in glomeruli of patients with MN but not in those with MCD or in those with normal kidneys. AR was minimally detected in biopsy specimens from patients with IgA nephropathy and sort 2 diabetes, whereas SOD2 wasn't detected in these patients. The mechanism and trigger for the "neoexpression" of those antigens in podocytes aren't known but is also a results of an initial injury mediated by pathogenic antibody deposition like anti-PLA2R, possibly driven by oxidative stress. These important breakthroughs in identifying target antigens in human MN opens the door to understanding the role of those autoantibodies and antibodies within the pathogenesis of primary MN.

Whereas the character of the immune complex deposits in MN requires further study, the mechanisms resulting in the proteinuric and nephrotic state are better understood. this understanding of those mechanisms is essentially supported data emerging from studies of Heymann's nephritis. during this model, immune complex formation within the subepithelial zone initiates activation of the complement pathway resulting in the formation of the C5b-C9 membrane attack complex. This leads to complement-mediated injury to the epithelial cells. The proposed sequence of events includes complement activation and sublytic complement C5b-9 attack on podocytes leading to upregulated expression of genes for the assembly of oxidants, proteases, prostanoids, growth factors, animal tissue protein, TGF, and TGF receptors resulting in overproduction of extracellular matrix. C5b-9 also causes alterations of the cytoskeleton that cause abnormal distribution of slit diaphragm proteins and detachment of viable podocytes. These events end in disruption of the functional integrity of the GBM and also the protein filtration barrier of podocytes.

Complement activation also leads to tubular somatic cell injury and mediates progressive interstitial disease in MN. Proteinuria itself may result in tubulointerstitial damage through activation of the choice complement pathway. Strong staining for properdin, a soluble complement regulator also referred to as complement factor P, on the luminal surface of the tubules was observed in kidney biopsy specimens from patients with primary MN but not from healthy kidney donors.

The human leukocyte antigen (HLA) class II antigen DR3 has been linked with MN,

and its presence is related to a relative risk of 12. during a Japanese population, there's an increased frequency of HLA-DR2 and HLADQW1 in patients with MN. it'd be possible that a haplotype containing HLA-DR3 and specific HLA class I antigens is also common in these patients also.

Recent studies have suggested a viable role for APOL1 risk alleles in increasing risk or accelerating progression of PLA2R-associated MN in association with collapsing nephropathy.

LABORATORY FINDINGS

Urinalysis , the liquid biopsy is very essential for MN cases . The following findings can be seen in a nephrotic syndrome patient with MN :

1.Urine albumin – 3+ or 4+

2.hematuria is very rare if present there will be dysmorphic rbcs.

3.lipid casts due to profound lipiduria . Infact nephrotic syndrome was called as lipoid nephrosis

Proteinuria is that the hallmark of MN. Nearly 80% of MN patients excrete nearly 3 g of protein for twenty-four hours. In some patients, the number of urinary protein may exceed beyond 20 g/day. A Medical Research Council study reported that 30% of patients with MN excreted over 10 g of protein per day at the time of presentation. Microscopic hematuria , defined as the presence of more than 3 rbcs per high power field , is present in 30% to 50% of patients at the time of presentation. On the opposite hand, Macroscopic hematuriais distinctly uncommon and occurs in but 4% of adult patients, although it should be common in paediatric population. Most patients

have either normal or only slightly decreased kidney function. In fact, impaired renal function is found in but 10% of patients at the time of presentation. In patients with severe nephrotic syndrome, hypoalbuminemia is common, as is that the loss of other serum proteins, including IgG. Serum lipoprotein levels are elevated, as in other sorts of nephrotic syndrome. Elevated levels of LDL and VLDL are common in MN. In one study, elevated levels of lp(a) normalized in patients whose disease was inactive.

Levels of complements C3 and C4 are typically normal in patients with MN. The complex of terminal complement components referred to as C5b-9 is found within the urine of some patients with active MN. there's increased excretion of this complex in patients with active immune complex formation. The excretion may decrease during disease inactivity.

To exclude common causes of secondary MN, one should order serologic tests for infections like serum hepatitis, viral hepatitis, and syphilis, further as tests for immunologic disorders like lupus, mixed CTD, and cryoglobulinemia. MN has been related to graft-versus-host disease (GVHD) following allogeneic somatic cell transplant(ASCT), and this could even be considered .

Although thrombophilia appears to be present in patients with syndrome in common, this tendency is also high in patients with MN. the precise mechanisms resulting in thrombophilia in these group of patients are poorly understood. Patients with MN have hyperfibrinogenemia with increased levels of circulating procoagulants and decreased levels of anticoagulant factors like antithrombin

III.The thrombotic tendency could also be increased by the polycythemia that happens in some patients, further as by the effect of Lp(a) to retard thrombolysis. Other possible contributors to the thrombophilic state include volume depletion, diuretics and steroid use, venous stasis, immobilization, and immune complex activation of the clotting cascade and anti–α-enolase antibodies. vena thrombosis is reported more frequently in patients with MN than in those with syndrome thanks to other causes. The prevalence of all kinds of deep vein thrombosis in patients with MN ranges from 9% to 44%. The combined burden of deep vein and venous blood vessel thrombosis has been estimated to be as high as 45%. vena renalis thrombosis is usually silent, with embolism being its first presenting sign. the chance of venous thromboembolic events appears to be higher when the albumen concentration is a smaller amount than 2.5 g/dL, and such events occur in as many as 40% of those patients. it's the priority for the morbidity and, at times, mortality related to embolism that has led to the utilization of prophylactic anticoagulation for patients with severe nephrotic syndrome and MN. a call analysis suggested that the danger of life-threatening complications of embolism outweighed the risks related to anticoagulant therapy. However, this analysis could also be supported an overestimate of truth incidence of thromboses among patients with MN. No direct controlled data are available to support or refute such a contention.A retrospective analysis of a treatment regimen to forestall venous thromboembolism in 143 patients with syndrome (low-molecular-weight heparin or low-dose heparin for patients with albumin but 2.0 g/dL and aspirin 75 milligram daily for patients with albumin 2.0 to 3.0 g/dL) looked as if it would be

effective with only a few complications.(479) Unfortunately, there's no direct controlled support for the routine use of prophylactic anticoagulation in patients with primary MN; however, the case can be made for the judicious use of warfarin in patients with severe nephrotic syndrome who have a profoundly decreased albumin level (probably <2 milligram/ dL) if no contraindications are present. Randomized, controlled trials are warranted.

Light Microscopy

The characteristic histologic abnormality by light microscopy is diffuse global capillary wall thickening within the absence of great glomerular hypercellularity . Light microscopic features of MN, vary with the stage of the disease and with the degree of secondary chronic sclerosing glomerular and tubulointerstitial injury. Mild stage I lesions might not be discernible by light microscopy, especially when only H&E stain is employed. Stage II, III, and IV lesions usually have readily appreciable thickening of the capillary walls.

Special stains that accentuate basement membrane material, like the Jones' methenamine silver stain, may reveal the basement membrane changes that are induced by the subepithelial immune deposits. Spikes along the outer aspect of the GBM usually are seen in stage II lesions . Stage III and IV lesions have irregularly thickened and trabeculated basement membranes, which resemble changes that occur with MPGN and chronic thrombotic microangiopathy.

Overt mesangial hypercellularity isn't common in primary MN, although it's more frequent in secondary MN.Crescent formation is rare unless there's concurrent anti-GBM disease or ANCA disease.

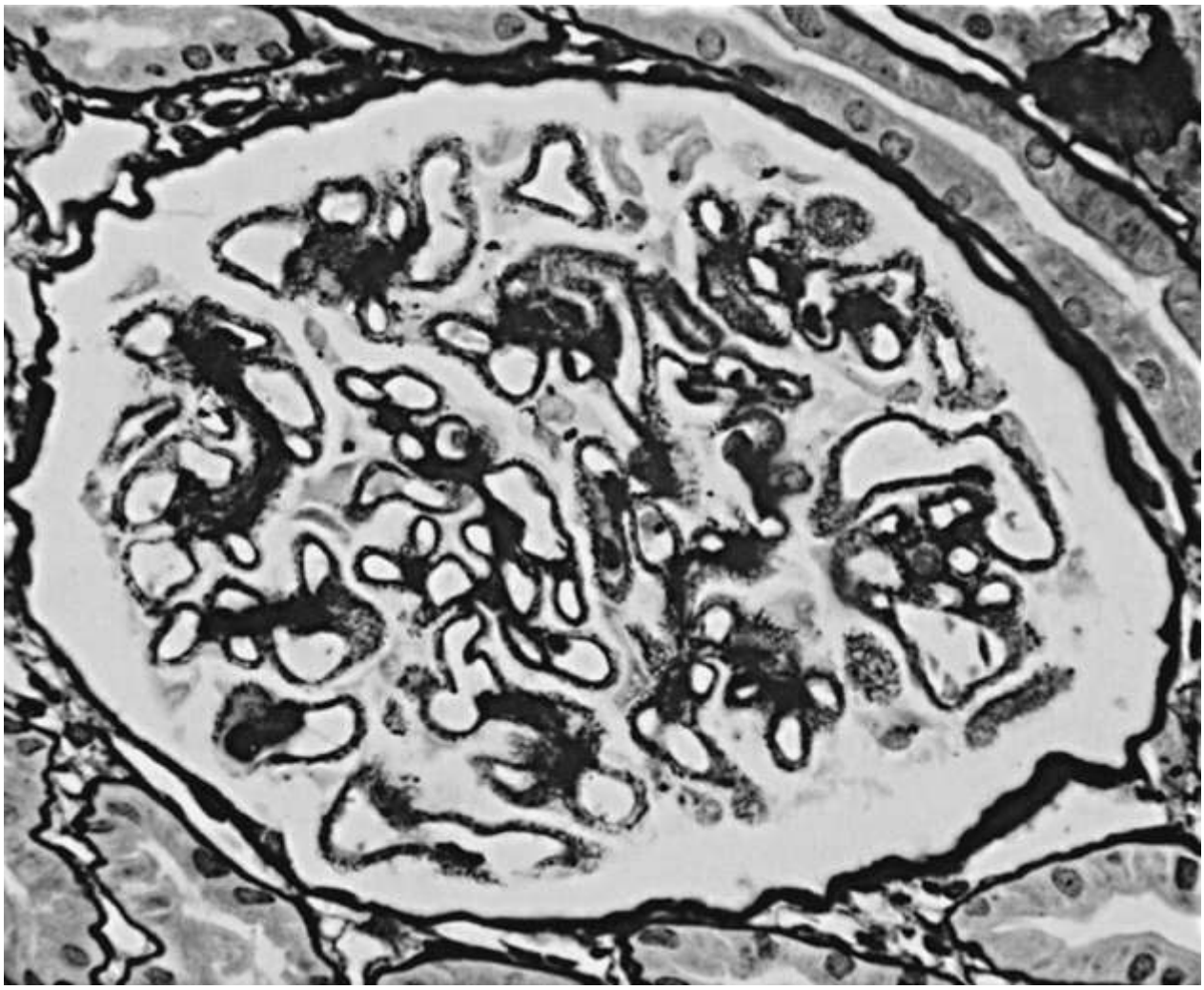


FIGURE: Light micrograph of a glomerulus with features of stage II membranous nephropathy demonstrating spikes along the outer aspects of the glomerular basement membrane. These correspond to the projections of basement membrane material between the immune deposits. (Jones' methenamine silver stain, ×300.)

With disease progression, chronic sclerosing glomerular and tubulointerstitial lesions develop. Glomeruli become segmentally and globally sclerotic and develop adhesions to Bowman's capsule. Worsening tubular atrophy, interstitial fibrosis, and interstitial infiltration by mononuclear leukocytes parallels to progressive loss of renal function.

Immunofluorescence Microscopy

The characteristic immunofluorescence microscopy finding in MN is diffuse global granular capillary wall staining for immunoglobulin and complement . IgG is that the most frequent and typically the foremost intensely staining immunoglobulin, although less pronounced staining for IgA and IgM is common . IgG4 is that the most prominent IgG subclass within the capillary wall deposits of primary MN. C3 staining is present over 95% of the time but typically is comparatively low intensity. C1q staining is rare and of low intensity in primary MN but is frequent and of high intensity in lupus MN.

Pathologic Features of Nonlupus Membranous Nephropathy*,	
	Feature Present (%)
Immunofluorescence Microscopy	
Immunoglobulin G	99 (3.5+)
Immunoglobulin M	95 (1.2+)
Immunoglobulin A	84 (1.1+)
C3	97 (1.6+)
C1q	34 (1.1+)
κ-light chain	98 (3.1+)
λ-light chain	98 (2.8+)
Electron Microscopy	
Subepithelial electron-dense deposits	99
Mesangial electron-dense deposits	16
Subendothelial electron-dense deposits	7
Endothelial tubuloreticular inclusions	3
Stage I	38
Stage II	32
Stage III	6
Stage IV	5
Stage V	1

Mixed stage	20

*Based on an analysis of 350 consecutive kidney biopsy specimens from patients with nonlupus membranous nephropathy evaluated at the University of North Carolina Nephropathology Laboratory.

†Values in parentheses indicate mean intensity of positive staining on a scale of 0 to 4+.

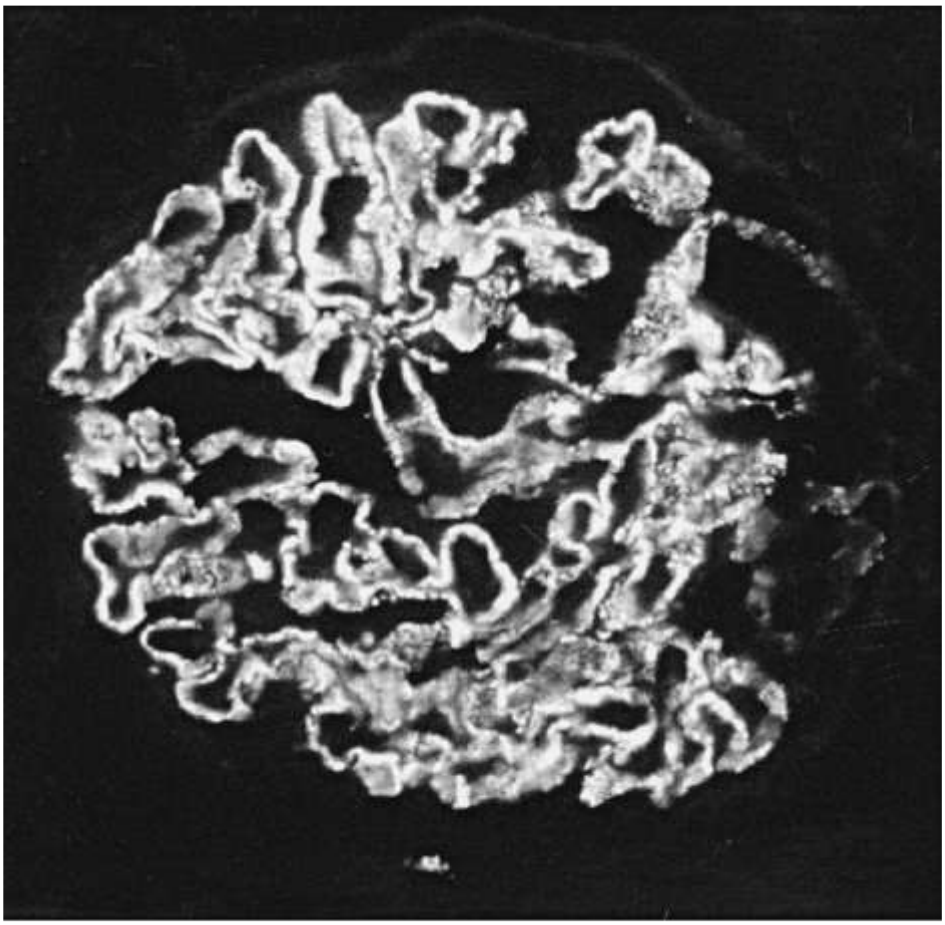


FIGURE: Immunofluorescence micrograph showing global granular capillary wall staining for immunoglobulin G (IgG) in a glomerulus with membranous nephropathy. (Fluorescein isothiocyanate anti-IgG stain, ×300.)

Although terminal complement components (i.e., components of the membrane attack complex) aren't usually evaluated in routine diagnostic preparations, there's very intense staining of the capillary walls for these components. In some patients who have concurrent anti-GBM glomerulonephritis and MN, linear staining for IgG is discerned slightly below the granular staining. Tubular basement membrane staining for immunoglobulins or complement is rare in primary MN, but it's common in secondary MN, especially lupus MN.

Electron Microscopy

The pathologic hallmark of MN is that the presence of subepithelial immune complex deposits or their structural consequences. microscopy gives us the foremost definitive diagnosis of MN, although a comparatively good diagnosis will be made supported typical light microscopic and immunofluorescence(IF) microscopic findings. . The earliest ultrastructural manifestation, stage I is characterized by the presence of scattered or regularly distributed small immune complex–type electron-dense deposits within the subepithelial zone between the basement membrane and also the podocyte. Podocyte process effacement and microvillous transformation occur altogether stages of MN when there's substantial proteinuria. Stage II is characterized by projections of basement membrane material round the subepithelial deposits. In three dimensions, these projections surround the edges of the deposits, but when observed in cross section, they seem as spikes extending between the deposits . In stage 3, the new BM material surrounds the deposits and in cross section there's basement membrane material between the deposits and therefore

the epithelial cytoplasm . At now the deposits are intramembranous instead of sub epithelial .StageIV is characterized by the loss of the electron density of the deposits which regularly ends up in irregular electron-Lucent zones within an irregularly thickened basement membrane.Although not described by Churg and Ehrenreich some nephropathologists recognize stageV which is characterized by a repaired outer basement membrane zone with the sole residual basement membrane disturbance within the inner aspect of the basement membrane

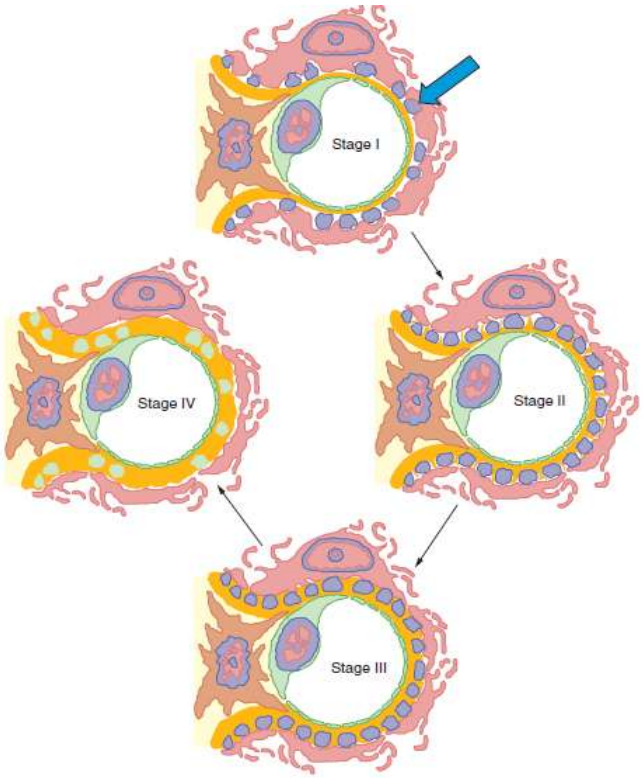


Figure : Diagram depicting the four ultrastructural stages of membranous nephropathy

. Stage I – Subepithelial dense deposits without adjacent basement membrane reaction

. Stage II - Projections of basement membrane adjacent to deposits.

Stage III – Deposits surrounded by basement membrane.

. Stage IV - Thickened basement membrane with irregular lucent zones.

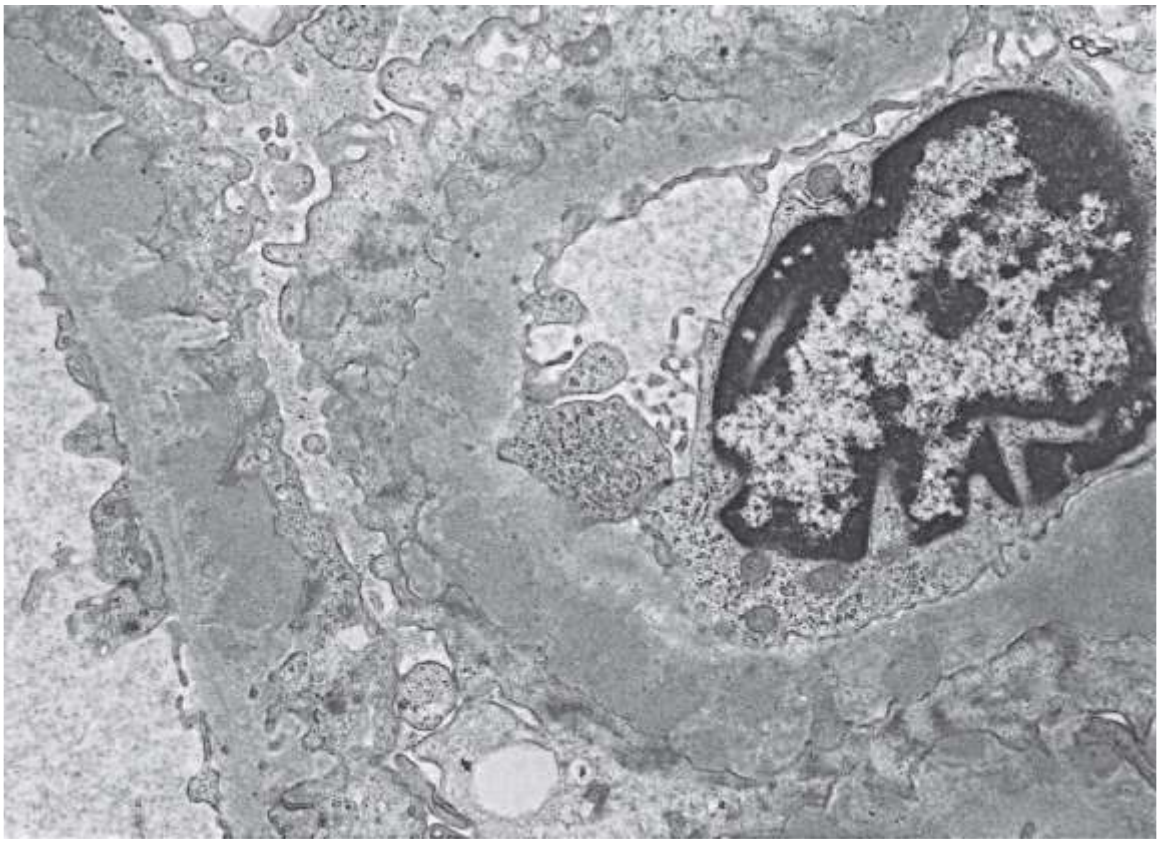
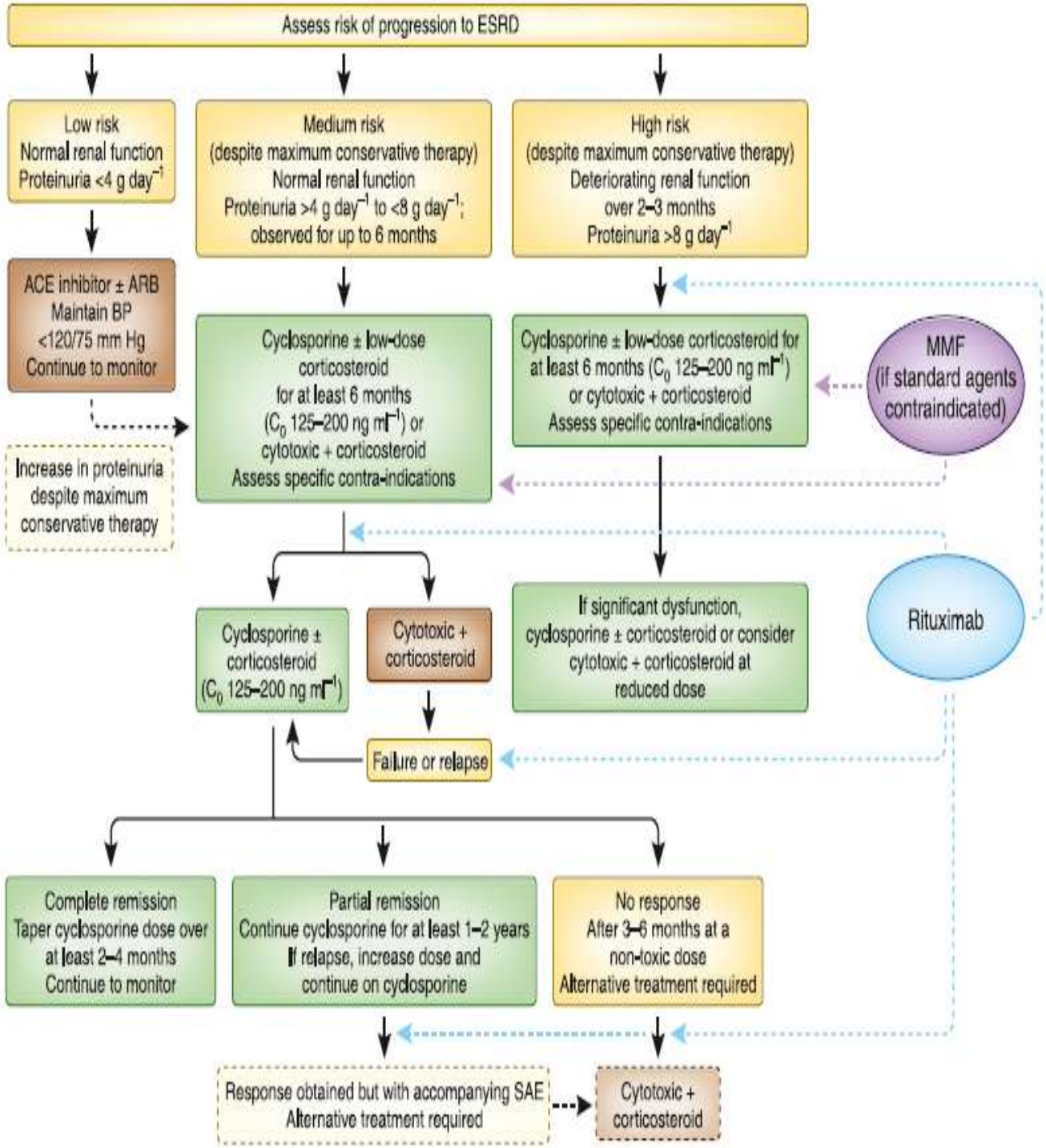


Figure : Electron micrograph showing features of stage II membranous nephropathy with numerous subepithelial dense deposits (*arrows*) and adjacent projections of basement membrane material.

Mesangial dense deposits are rare in primary MN but are more frequent in secondary MN .This suggests that primary MN is caused by subepithelial in place immune complex formation with antibodies from the circulation combining with antigens derived from the podocyte. Immune complexes formed only at this site couldn't go against the direction of filtration to achieve the mesangium. Secondary varieties of MN usually are caused by immune complexes that contain

antigens that are within the circulation, like antigens derived from infections (like hepatitis B), tumor antigens (e.g., colon cancer), or autoantigens (ex. thyroglobulin). With both the antigens and also the antibodies within the circulation, it's more likely that some immune complexes would form that may localize not only within the subepithelial zone but also within the mesangium or subendothelial zone. this is often demonstrated within the secondary style of MN that happens in patients with SLE. In over 90% of lupus MN specimens, mesangial dense deposits are identified by microscopy. Therefore, the presence of mesangial dense deposits should raise the index of suspicion for secondary instead of primary MN.

TREATMENT PROTOCOL



Inspite of the actual fact that MN could be a relatively common glomerular disease and has been subjected to multiple randomised trials of varied combinations of steroids and immunosuppressive drugs , the therapy of MN remains controversial. Multiple factors complicate the interpretation of such studies. These include the limited number of cases or short duration of the studies, and therefore the disability to include the benefits of current non specific therapies like achieving good BP control, or medications that may decrease the level of urinary protein excretion (such as ACE inhibitors or ARBs)

Treatment that don't seem to be disease specific :

Non disease specific variables have been shown to affect the prognosis of all glomerular diseases adversely, including Membranous Nephropathy. Combinations of BP control to values of but 125/75 mmHg, dietary salt restriction, diuretics, and therefore the angiotensin converting enzyme inhibitors (ACE inhibitors), and angiotensin receptor blockers (ARBs) are appropriate for all patients with MN.

BP reduction :

Blood pressure management is of utmost importance in MN patients . Reduction of BP to less than 125/75 reduces the progression of renal failure and also decreases the proteinuria. Other end organ damage due to hypertension can also be reduced. The following antihypertensives can be used in the order of preference:

1.ACE inhibitors / ARBs

2.Aldosterone antagonist

3.CCBs , Beta blockers

4.Central sympatholytics and alpha blockers.

Treatment of hyperlipidemia :

The hyperlipidemia is hallmark of nephrotic syndrome . it is characterised by increase in LDL , IDL , VLDL cholesterol levels and decrease in HDL cholesterol . the serum triglyceride levels are also increased.It is treated with the following drugs :

1.Statins – decrease LDL ,triglycerides , modest rise in HDL eg. Atorvastatin , simvastatin , pravastatin , rosuvastatin etc.

2.Fibrates like clofibrate and gemfibrozil . they decrease the triglyceride levels , better avoid combining with statins due to more risk of rhabdomyolysis.

3.Nicotinic acid – it raises the HDL levels and modestly decreases the triglyceride levels

4.Ezetimibe – inhibits cholesterol absorption from intestine

5.cholesterol binding resins like cholesevalam.

Low protein diet :

The excretion of protein in urine occurs via the transtubular migration of the proteinuria .The excretion of proteins and lipids itself can worsen renal function through various mechanisms , hence warranting antiproteinuria measures . Studies show that moderate protein restriction to 0.8mg per kg per day can cause 15 to 20 percent reduction of proteinuria .Vegetable protein is mostly preferred to that of animal protein. While on the other hand , patients with ESRD must receive high protein diet of 1.5 mg per kg per day because they have increased protein catabolism and protein loss due to diabetes.

The use of ACE inhibitors and ARBs :

ACE inhibitors and ARBs is a cornerstone of membranous nephropathy because it has significantly reduced the need for immunosuppression in MN patients.It acts via the following mechanisms :

1.Reduction of proteinuria

2.Alters renal hemodynamics by reducing the intraglomerular pressure there by reducing the progression of renal failure.

3.Decrease in salt and water retention.

The use of prophylactic anticoagulation:

MN patients have non selective proteinuria , hence there is excretion of protein c , protein s and anti thrombin 3. Hence it leads to a procoagulant state , any how use of prophylactic anticoagulation is not warranted in such patients through multiple randomised multicentered trials.Prophylactic anticoagulation can be considered in the following patients:

1.prolonged immobilisation

2.abdominal , pelvic and gynaecological surgeries

3.severe cardiac failure

4. liver failure

Unfractionated heparin is preferred and warfin is preferred in MN patients , target INR is 2-3. NOACs like dabigatran and apixaban are under trial.

Disease-specific therapy:

Patients who do not respond to standard non specific medications and conservative approach , pts with progressive renal failure and worsening proteinuria are candidates of disease specific therapy. Immunosuppression is the mainstay of therapy because it is known that the main pathogenesis is autoimmunity.Through out the ages , since 1950s various immunosuppressant drugs are tried either alone or in combination with varying levels of success, which will be discussed now.

CORTICOSTEROIDS:

Steroids were tried for IMN patients since the autoimmune hypothesis was proposed .Initially steroids were given as monotherapy which showed significant decrease in proteinuria and decrease in the progress of renal failure. The remission rate was 60 percent .But long term follow up revealed nearly fifty percent of patients who underwent remission with steroids had a relapse after 2 years. Also initially the regimens contained high dose of steroids [1.5 to 2 mg /kg /day], prolonged high dose of steroids lead to many complications like worsening of hypertension , diabetes , cushingoid facies , skin striae , osteoporosis , proximal muscle weakness , skin infections , tuberculosis and other side effects of steroids.There was a shift of paradigm after Ponticelli et al introduced a new regimen which contained combination of steroids and other immunosupressants like cyclophosphamide , chlorambucil .The complications of steroids were significantly reduced , the remission rate increased and the relapse rate decreased.

MODIFIED PONTICELLI REGIMEN

Although there are plenty of studies using steroid and immune-suppressive regimens, the treatment of MN remains controversial. per few authors, there's no need for a selected treatment because the clinical course of the disease is stable, whilst others suggest treating patients using medicine protocols.

Two controlled studies demonstrated that administering steroids alone wasn't effective enough for the treatment of MN . Immuno-suppressive drugs are used for the treatment of membranous nephropathy for adults since 1986. These agents (like chlorambucil, cyclophosphamide) reduce proteinuria and results in significant long-term recovery of renal survival.

The combination of oral steroids and cytotoxic drugs is another approach. it's the simplest and also the most generally accepted Ponticelli regimen. This regimen involves a 6-month cyclic change, methylprednisolone (1 g IV/day for 3 days) is run, which is followed by oral prednisolone for 1 month and oral cyclophosphamide for the subsequent month . In Ponticelli's study, it had been observed that 10% of the treatment group and 50% of the control group developed failure and 4 of 39 patients within the control group and 1 of 42 patients within the treatment group needed dialysis at the tip of 5-year follow-up. At the tip of the 10-year follow-up period, 88% of the treatment group and 47% of the control group developed complete remission or partial remission of syndrome. 8 per cent of the treatment group and 40% of the control group had kidney failure .

IMMUNOSUPPRESSION

Immunosuppressive drugs that have received attention for IMN include alkylating agents like cyclophosphamide , chlorambucil, calcineurin inhibitors (CNIs) like cyclosporine, tacrolimus, mycophenolate mofetil (MMF), rituximab, and corticotrophin (ACTH). there's lack of well powered, RCT that formally compare therapies. the standard of the prevailing evidence for these different regimens in IMN is variable. Comparisons among studies are hampered by differences within the risk profile of the patients and variable duration of follow-up, among other factors.

Alkylating Agents

Ponticelli et al. and Jha et al. used a 6-month regimen consisting of daily oral chlorambucil or cyclophosphamide, alternating monthly with steroids .Their patients had nephrotic-range proteinuria and normal renal function. Conversely, investigators from Netherlands have described outcomes of an extended course, typically 12 months of daily oral cyclophosphamide and corticosteroids in patients with syndrome and deteriorating kidney function.

Both Ponticelli et al. and Jha et al. discovered that alternating monthly cycles of corticosteroids and alkylating agent were more practical than supportive therapy alone for inducing remissions of proteinuria and preserving kidney function. Ponticelli et al. discovered that substitution of cyclophosphamide for chlorambucil provides similar efficacy with an improved adverse side effect profile. Jha et al. allowed crossover to the immunosuppressive treatment arm months after randomization to supportive treatment. it's noted that remission

rates were lower among patients who switched to immunosuppression as rescue therapy (47%) than among the patients who were initially randomized to immunosuppression (72%), suggesting that delay in immunosuppressive therapy until evidence of disease progression diminishes efficacy.

Studies reported by du Buf-Vereijken et al. and Hofstra et al. from Netherlands provide additional insights into the effect of delaying medicine therapy for IMN until there's evidence of renal function deterioration. These investigators favor this restrictive treatment policy because it identifies patients at highest risk of progression and avoids unnecessary immunosuppression in patients with a more favorable prognosis. A beneficial effect of this approach in attenuating deterioration of renal function was shown within the case-controlled study of high-risk IMN patients reported by du Buf-Vereijken et al. Renal outcomesof 65 patients treated for 1 year with oral cyclophosphamide and steroids were compared with 24 matched control patients. Control patients received either no immunosuppression or treatments that have subsequently proven to be ineffective (prednisone monotherapy, intravenous cyclophosphamide, or both). Patients had an impaired GFR at baseline (median creatinine clearance of 42 ml/min per 1.73m2) and high-grade proteinuria. Remission of proteinuria was achieved in 86% of 65 patients receiving immunosuppressivetherapy

Table 1. Immunosuppressive regimens that have been used in treatment of IMN

Immunosuppression Agent	Regimen
Alkylating agents	Italian Ponticelli protocol
	Months 1, 3, and 5: 1 g/d intravenous methylprednisolone for 3 consecutive d, followed by oral prednisolone 0.4 mg/kg daily or oral prednisone 0.5 mg/kg daily for 27 d
	Months 2, 4, and 6: 0.2 mg/kg oral chlorambucil daily for 30 d
	Modified Ponticelli protocol
	Months 1, 3, and 5: 1 g/d intravenous methylprednisolone for 3 consecutive d, followed by oral prednisone 0.5 mg/kg daily for 27 d
	Months 2, 4, and 6: 2–2.5 mg/kg oral cyclophosphamide daily for 30 d
	Dutch protocol[34]
	1.5–2 mg/kg oral cyclophosphamide daily for 12 mo plus 0.5 mg/kg oral prednisone daily or every other day for 6 months and then tapered, plus 1 g/d intravenous methylprednisolone for 3 consecutive days for months 1, 3, and 5
Cyclosporine, tacrolimus	3.5 mg/kg cyclosporine daily, achieving levels of 125–200 μg/L for a minimum of 6–12 mo, then tapered to lowest possible maintenance dose (± low-dose corticosteroids)
	0.05 mg/kg tacrolimus daily achieving levels 7–9 for 6–12 mo, then tapered to lowest possible maintenance dose (± low-dose corticosteroids)
MMF	2 g/d MMF for 1 yr ± low-dose corticosteroids
Rituximab	375 mg/m^2 weekly for four doses
	1 g on days 1 and 15
	375-mg/m^2 single doses, titrated to the number of circulating B cells
ACTH	1 mg tetracosactrin injected intramuscularly twice weekly for 6–12 mo
	80 U corticotropin injected intramuscularly twice weekly for 6–12 mo

Table 2. Selected studies of alkylating agents in patients with IMN

Study	N	Treatment Regimen	Follow-Up	Initial Remission Rate			Relapse Rate (Timing)	Effect on Renal Survival
				CR	PR	Total		
Ponticelli et al. (1989 and 1995)[39,40]	42	Months 1, 3, and 5: steroids[a]; months 2, 4, and 6: 0.2 mg/kg chlorambucil daily	Up to 10 yr	57 (24/42)	24 (10/42)	81	24 (8/34)	Dialysis-free 10-yr survival: 92
	39	No immunosuppression		18 (7/39)	15 (6/39)	33	31 (4/13)	Dialysis-free 10-yr survival: 60
Ponticelli et al. (1998)[43]	44	Mo 1, 3, and 5: steroids[b]; months 2, 4, and 6: 0.2 mg/kg chlorambucil daily	Median 3 yr	27 (12/44)	55 (24/44)	82	31 (11/36) (between 6 and 30 mo)	1 patient (2%) reached ESRD after 42 mo
	43	Mo 1, 3, and 5: steroids[b]; months 2, 4, and 6: 2.5 mg/kg cyclophosphamide daily	Median 3.5 yr	37 (16/43)	56 (24/43)	93	25 (10/40) (between 6 and 24 mo)	2 patients (4%) reached ESRD after 36 mo
Jha et al. (2007)[41]	47	Mo 1, 3, and 5: steroids[c]; months 2, 4, and 6: 2 mg/kg cyclophosphamide daily	Median 11 yr	32 (15/47)	40 (19/47)	72	24 (8/34)	10-yr dialysis- free survival: 89
	46	No immunosuppression	Median 11 yr	11 (5/46)	24 (11/46)	35	25 (4/16)	10-yr dialysis-free survival: 65
du Buf-Vereijken (2004)[34] (not randomized; matched historical comparison)	65	1.5–2 mg/kg oral cyclophosphamide daily for 12 mo plus steroids[d]	Median 4.3 yr	26 (17/65)	60 (39/65)	86	20 (11/56)	5-yr dialysis- free survival: 86
	24	No treatment or various immunosuppressive agents subsequently considered ineffective		NA	NA	NA	NA	5-yr dialysis-free survival: 32
Hofstra et al. (2010)[42]	14	Early start. 1.5 mg/kg oral cyclophosphamide daily for 12 mo plus steroids[c]	Mean 6 yr	64 (9/14)	29 (4/14)	93	23 (3/13) (median 36 mo after treatment)	1 patient (7%) reached ESRD
	12	Late start. 1.5 mg/kg oral cyclophosphamide daily for 12 mo plus steroids[c]	Mean 6 yr	67[e] (8/12)	25 (3/12)	92	27% (3/11) (median 38 mo after treatment)	0 patients reached ESRD

Data are expressed in percentages unless otherwise indicated. CR, complete remission; PR, partial remission; NA, data not available.

[a]Dosages at months 1, 3, and 5: 1 g intravenous methylprednisolone daily for 3 days, followed by 0.4 mg/kg oral prednisolone daily or 0.5 mg/kg prednisone daily for 27 d. Dosage at mo 2, 4, 6: 0.2 mg/kg chlorambucil daily.

[b]Dosages at months 1, 3, and 5: 1 g intravenous methylprednisolone daily for 3 days, followed by 0.4 mg/kg oral prednisolone daily for 27 d.

[c]Dosages at months 1, 3, and 5: 1 g intravenous methylprednisolone daily for 3 days, followed by 0.5 mg/kg oral prednisolone (or prednisone) daily.

[d]Dosages at months 1, 3, and 5: 1 g intravenous methylprednisolone daily for 3 days, followed by 0.5 mg/kg oral prednisone every other day for 6 mo and then tapered.

[e]Includes four spontaneous remissions that occurred during the observation period.

At 5 years, a renal survival advantage was evident in cyclophosphamide -treated patients compared with controls (86%versus 32%; P,0.001). The renal survival of those cyclophosphamide -treated patients at 7 years was 74%, which is somewhat below the 10-year renal survival of patients with normal baseline renal function treated with a medicine regimen by Ponticelli et al.(92%) Hofstra et al. recently reported the results of atiny low , elegant study comparing early versus late initiation of immunosuppressive treatment. Patients were randomized to receive oral cyclophosphamide for 12 months plus corticosteroids early after diagnosis (n=14) or later if renal function deteriorated (n=12), defined as a rise of serum creatinine 25% reaching grade of 135 umol/L or a rise of serum creatinine 50%. within the late treatment arm, 67% of patients ultimately met criteria for immunosuppression after a median of 14 months from randomization. Overall cumulative incidence of remission was similar in both the first and late treatment arms (93% versus 92%, respectively) but earlier treatment resulted in more rapid onset of remission. Relapse rates were similar. At final follow-up (mean 72 months), there have been no differences in clinical status, proteinuria, or Kidney function in either group, with the latter observation indicating that immunosuppressive treatment led to an improvement in renal function within the late treatment arm . the nice overall outcomes do provide reassurance that delaying therapy is justified in some patients. By delaying treatment, 33% of patients avoided unnecessary exposure to immunosuppression. However, delayed treatment was related to more frequent and severe side effects and more hospitalizations. An individualized

approach that considers age, pre-existing comorbidities, and risk of treatment versus risk of complications of the syndrome is critical when deciding therapy. In spite of the favorable results with alkylating agents, there's reluctance to prescribe them thanks to the short-term and long-term adverse effects. Short-term effects include myelosuppression, leucopenia infections, hemorrhagic cystitis, and gastrointestinal effects like peptic ulcers, nausea, anorexia, and liver dysfunction. Risk of infertility remains a priority for patients in childbearing years. Cancer risk remains a long-term worry, particularly since the cumulative dosage of cyclophosphamide increases if repeat courses are needed after relapse. The Ponticelli regimen entails 3 months of cyclophosphamide (2 milligram/kg daily), which may be a cumulative dose of roughly 13 g during a 70-kg patient. The 12-month regimen using 1.5milligram/kg daily represents a cumulative dose of roughly 40 g in an exceedingly 70-kg patient. Several studies have reported threshold values for cumulative doses of cyclophosphamide, above which is related to increased risk of malignancies like bladder cancer, skin malignancy, and lymphoproliferative disorders. Older studies report an increased risk of malignancy with cumulative doses 50 g, whereas recent studies suggest that exposure to lower cumulative dosages may cause an increased risk.

CALCINEURIN INHIBITORS

Cyclosporine is a longtime option for treatment of IMN patients at moderate or high risk of disease progression. Tacrolimus, another CNI, is another. Cumulative data indicate that CNIs are effective in inducing a remission of proteinuria in up to 80% of

patients .They show favorable responses in patients who are unresponsive to other immunosuppressants, including alkylating agents. in an exceedingly recent RCT during which all. patients had previously failed the Ponticelli protocol, treatment with cyclosporine for two years (plus low-dose prednisone) led to remissions in nearly 80% of patients and stabilization of kidney function.

The antiproteinuric effect of CNIs are typically evident early. Generally, if response to proteinuria isn't present by 3 months, it's unlikely that a big response will occur later. However, time to maximum reduction of proteinuria takes longer. Although desired duration of therapy has not been established, extended therapy for a minimum of one year is suggested for patients who show an initial response to those agents, because the quantity of remissions and proportion of complete remissions increases with duration of treatment. the bulk of complete remissions with CNIs occur after 6 months of therapy and also the number increases as treatment continues for 12 months.

The role of CNIs in attenuating a decline in renal function and also the long-term effect on renal survival in MN are less clear because of lack of longitudinal studies. During a study design almost like that utilized by du Buf-Vereijken et al. 65 patients with IMN were initially followed conservatively for 12 months. Only patients with clear evidence of declining RFT and protracted nephroticrange proteinuria during the observation period were randomized to receive treatment with cyclosporine for 1 year or placebo. Of 65 patients, 23 (36%) met criteria for randomization. Compared with placebo, cyclosporine-treated patients demonstrated significantly reduced proteinuria (halving of proteinuria in 50% of treated

patients versus no improvement in placebo patients) and slower rates of decline in renal function as measured by change within the slope of creatinine clearance. These improvements were sustained in 75% of the patients for up to 2 years post-treatment. Fewer patients within the treated group progressed to ESRD (11% versus 50%, respectively.

A recent multicenter RCT from China compared efficacy of tacrolimus with a course of cyclophosphamide in 73 patients with IMN. 50 Patients were randomized to receive tacrolimus for 9 months or 4 months of daily oral cyclophosphamide (100 milligram/d). Both groups received oral prednisone. Cumulative remission rates at 6 months were greater within the tacrolimus arm than the cyclophosphamide arm (85% versus 65%, P,0.05); however, remission rates were comparable by 1 year. Relapse rates between the 2 groups were similar (18% versus 23%), leading the authors to conclude that short-term efficacy of tacrolimus plus steroids can be better than cyclophosphamide plus steroids. Several issues limit the conclusions which will be drawn from this study. Tacrolimus wasn't compared with one in every of the quality cyclophosphamide -containing regimens. Follow-up was very short, which can underestimate the true relapse rates. Last, there have been inconsistent use of ACE inhibitors and ARBs, which favored the tacrolimus group. Currently, there's a three-arm randomized controlled trial ongoing within the U.K that compares supportive therapy versus 1 year of cyclosporine versus 6 months of alternating prednisolone/chlorambucil in patients with progressive IMN.

Rituximab

Of the newer drugs being explored for IMN, rituximab has emerged because the possibly candidate to be included into treatment guidelines. Although it's yet to be tested in RCTs and there's an absence of longitudinal data, important groundwork has been laid since its first reported use for IMN in 2002. Most of the reported experiences with rituximab are from uncontrolled pilot trials or case series from two centres in Bergamo, Italy, and also the Mayo Clinic within the u. s.. the subsequent treatment protocols are tried for IMN) 1. Four weekly doses of 375 milligram/m2, which is that the standard dosing for treatment of lymphoma; 2. Two 1000-milligram doses given biweekly, which is standard for rheumatoid arthritis; 3. B cell–driven protocol during which dosing is titrated to the quantity of circulating B cells.

Rituximab is a monoclonal antibody produced by hybridoma technique , it is an anti CD 20 antibody .CD 20 plays a major role in cell mediated and humoral immunity.Use of rituximab decreases the serum levels of antibodies against PLA2R.The lymphocytic infiltration around glomerulus is decreased.Other drugs of this class are :

1.obinituzumab

2.ofatumumab.

The pharmacokinetics of rituximab in nephrosis patients differ from that in nonproteinuric patients treated with identical protocols, prompting questions on the optimal dosing regimen for IMN. Compared with nonproteinuric patients, rituximab levels are lower and recovery of CD20-expressing B cells occurs earlier in nephrotic

patients. However, among nephrotic patients with IMN, the four-dose lymphoma and two-dose arthritis regimens seem to possess similar efficacy in spite of faster lymph cell recovery after the two-dose regimen. in step with these conclusions, a recent retrospective analysis of banked serum samples showed no detectable differences within the reduction of anti-PLA2R levels between the 2 dosing regimens. irrespective of the regimen administered, proteinuria tends to say no slowly and remissions may occur up to 2 years after treatment. Beck et al. showed that after administration of rituximab, the median time to achieve undetectable anti-PLA2R levels was 9 months (range, 1–18 months). this might explain the delay in remissions, the reduction in antibody levels seems to precede the decline in proteinuria by months it's interesting to notice that remissions still occur well after the tip of therapy with rituximab or alkylating agents; complete remissions will be seen. 12 months after the completion of those interventions. this is often in contrast to what's observed after cyclosporine or tacrolimus, within which typically no additional remissions occur once treatment stops.

Relapse rates after rituximab therapy are difficult to estimate given the limited longitudinal data. There are two published studies (n=31) that followed patients for up to 24 months and relapses were in frequent (6% and 13%, respectively). it's hoped that forthcoming studies with extended follow-up will provide adequate information. Such data may inform decisions regarding role and timing of repeat dosing.

Toxicity profile of rituximab.:

1. Acute infusion reactions like fever, chills, pruritus, and skin rash
2. potentially fatal reactions (e.g., acute respiratory distress syndrome, bronchospasm, angioedema, shock and myocardial infarction)
3. Potentially fatal mucocutaneous reactions (e.g., Stevens–Johnson syndrome and toxic epidermal necrolysis)
4. Rare cases of the devastating demyelinating central systema nervosum disease, progressive multifocal leukoencephalopathy.

MMF:

Encouraging results from early, uncontrolled series published a decade ago indicated a possible role of MMF within the management of high-risk patients with IMN. Subsequent studies have produced mixed results . A multicentre RCT from France reported cumulative remission rates after 1 year of MMF that were no different from conservative therapy (approximately 40%). Two studies suggested that treatment with MMF had similar efficacy as a regimen consisting of alkylating agents plus steroids.

Table 3. Selected randomized controlled trials of CNIs in patients with IMN and evolution of remissions over time

Study	n	Treatment (Total Duration)	Follow-Up (mo)	Remissions									Relapse Rate (n) [Time to Relapse]
				6 mo			12 mo			24 mo			
				CR	PR	Total	CR	PR	Total	CR	PR	Total	
Cattran et al. (2001)[51]	28	3.5 mg/kg cyclosporine daily (26 wk); target trough 125–225 μg/ml for 26 wk, then tapered for 4 wk plus 0.15 mg/kg prednisone daily	Up to 19	7 (2/28)	68 (19/28)	75	7 (2/28)	39 (11/28)	46	7 (2/28)[a]	32 (9/28)[a]	39[a]	48 (10/21) [within 12 mo of drug cessation]
	23	Placebo plus 0.15 mg/kg prednisone daily		4 (1/23)	17 (4/23)	21	4 (1/23)	9 (2/23)	13	4 (1/23)	9 (2/23)	13	40 (2/5)
Naumovic et al. (2011)[52]	10	3 mg/kg cyclosporine daily for 6 mo, then adjusted to achieve trough levels of 80–100 ng/ml (24 mo) plus 0.5 mg/kg prednisone daily for 8 wk, then tapered	36	0	50 (5/10)	50	10 (1/10)	40 (4/10)	50	40 (4/10)	40 (4/10)	80	13 (1/8) [within 12 mo of drug cessation]
	13	1.5–2 mg/kg azathioprine daily for 6 mo, then 50 mg daily (24 mo) plus 0.5 mg/kg prednisone daily for 8 wk, then tapered		7 (1/13)	77 (10/13)	84	0	92 (12/13)	92	31 (4/13)	62 (8/13)	92	42 (5/12) [within 12 mo of drug cessation]
Praga et al. (2007)[49]	25	0.05 mg/kg tacrolimus daily for 12 mo (trough level 5–8 ng/ml), then tapered over 6 mo (18 mo)	Up to 30	12 (3/25)	44 (11/25)	56	24 (6/25)	48 (12/25)	72	32 (8/25)[a]	44 (11/25)[a]	76[a]	47 (9/19) [within 12 mo of drug cessation]
	23	Conservative		9 (2/23)	4 (1/23)	13	17 (4/23)	4 (1/23)	21	13 (3/23)[a]	13 (3/23)[a]	26[a]	0
Chen et al. (2010)[50]	39	0.1 mg/kg tacrolimus daily for 6 mo; target trough 5–10 ng/ml, then adjusted for trough 2–5 ng/ml (9 mo) plus 1 mg/kg prednisone daily for 4 wk, then tapered over 8 mo	12	28 (11/39)	56 (22/39)	85	NA	NA	79	NA	NA	NA	18 (6/33) [within 3 mo of drug cessation]
	34	100 mg/d cytoxan (4 mo) plus 1 mg/kg prednisone daily for 4 wk, then tapered over 8 mo		26 (9/34)	38 (13/34)	65	NA	NA	69	NA	NA	NA	22 (5/23)

Data are expressed in percentages unless otherwise indicated. CR, complete remission; PR, partial remission; NA, data not available.

[a]Remission rates reported at 18 mo (24-mo remission status not provided).

Table 4. Selected studies of rituximab for IMN and evolution of remissions over time

Study	n	Treatment Regimen	Remissions									Relapse Rate (n) [Time to Relapse]
			6 mo			12 mo			24 mo			
			CR	PR	Total	CR	PR	Total	CR	PR	Total	
Remuzzi et al. (2002)[60] and Ruggenenti et al. (2003)[61,a]	8	Four doses of 375 mg/m^2 per wk	0	63 (5/8)[a]	63	0	63 (5/8)[a]	63	NA	NA	NA	NA
Cravedi et al. (2011)[64]	22[b]	375 mg/m^2 per wk for 4 wk or	0	0	0	18 (2/11)	45 (5/11)	63	27 (3/11)	45 (5/11)	72	13 (1/8) [within 24 mo]
		375 mg/m^2 for 1 wk; redosed when ≥5 B cells/mm^3	0	0	0	18 (2/11)	45 (5/11)	63	18 (2/11)	45 (5/11)	63	14 (1/7) [within 24 mo]
Fervenza et al. (2008)[65]	15	Two 1-g doses (on days 1 and 15); repeated at 6 mo if proteinuria > 3 g/d and CD19+B cells >15/μl	0	29 (4/14)	29	14 (2/14)	43 (6/14)	57	NA	NA	NA	NA
Fervenza et al. (2010)[66]	20	Four doses of 375 mg/m^2 per week; repeated at 6 mo	0	40 (8/20)	40	0	50 (10/20)	50	20 (4/20)	60 (12/20)	80	6 (1/16)

Data are expressed in percentages unless otherwise indicated. CR, complete remission; PR, partial remission; NA, data not available.
[a]Remission status was standardized for ease of comparison. CR defined as proteinuria <0.3 g/d; PR defined as proteinuria ≤3.5 g/d and a 50% reduction from peak value.
[b]Eleven patients were given rituximab as first-line therapy, and 11 patients were given rituximab as second-line therapy.

An Post-treatment relapse is problematic. within the trial by Branten et al., 57% of patients relapsed within 2 years and a few relapses occurred during active treatment. Of interest, relapse is additionally a priority after treatment with the older antimetabolite, azathioprine. A recent study showed that 12 months of azathioprine induced remissions in an exceedingly large percentage of patients who had previously been refractory to the Ponticelli protocol. However, within 6 months of azathioprine withdrawal, 33% relapsed.

Although the initial enthusiasm regarding MMF has decreased , there's surely an area for MMF within the treatment protocol of IMN. However, until more data becomes available, it's difficult to recommendMMF as initial therapy. It maybe an

inexpensive option for patients in whom toxicity of alkylating agents and high-dose steroids are a priority or when significant azotemia prohibits use of Cyclosporine . MMF has been used with some success as rescue therapy in patients proof against other immunosuppression and has also been tried as adjunctive therapy to avoid prolonged exposure to CNIs; however, the evidence is simply too limited to recommend routine use of MMF for these indications. Extended duration of treatment

Table 4. Selected studies of rituximab for IMN and evolution of remissions over time

Study	n	Treatment Regimen	Remissions									Relapse Rate (n) [Time to Relapse]
			6 mo			12 mo			24 mo			
			CR	PR	Total	CR	PR	Total	CR	PR	Total	
Remuzzi et al. (2002)[60] and Ruggenenti et al. (2003)[61,a]	8	Four doses of 375 mg/m^2 per wk	0	63 (5/8)[a]	63	0	63 (5/8)[a]	63	NA	NA	NA	NA
Cravedi et al. (2011)[64]	22[b]	375 mg/m^2 per wk for 4 wk or	0	0	0	18 (2/11)	45 (5/11)	63	27 (3/11)	45 (5/11)	72	13 (1/8) [within 24 mo]
		375 mg/m^2 for 1 wk; redosed when ≥5 B cells/mm^3	0	0	0	18 (2/11)	45 (5/11)	63	18 (2/11)	45 (5/11)	63	14 (1/7) [within 24 mo]
Fervenza et al. (2008)[65]	15	Two 1-g doses (on days 1 and 15); repeated at 6 mo if proteinuria > 3 g/d and CD19+B cells >15/μl	0	29 (4/14)	29	14 (2/14)	43 (6/14)	57	NA	NA	NA	NA
Fervenza et al. (2010)[66]	20	Four doses of 375 mg/m^2 per week; repeated at 6 mo	0	40 (8/20)	40	0	50 (10/20)	50	20 (4/20)	60 (12/20)	80	6 (1/16)

Data are expressed in percentages unless otherwise indicated. CR, complete remission; PR, partial remission; NA, data not available.
[a]Remission status was standardized for ease of comparison. CR defined as proteinuria < 0.3 g/d; PR defined as proteinuria ≤3.5 g/d and a 50% reduction from peak value.
[b]Eleven patients were given rituximab as first-line therapy, and 11 patients were given rituximab as second-line therapy.

(.12 months), and possibly the addition of oral corticosteroids, could also be necessary to realize greater antiproteinuric effects or to stop relapse. The optimal target dosing of MMF for IMN isn't known because the pharmaco kinetics of MMFin patients with hypoalbuminemia and nephrosis don't seem to be well

defined. it's possible that higher drug doses are needed to succeed in the therapeutic window.

ACTH

ACTH is one amongst the newer agents being explored for treatment of IMN. Historically, ACTH was accustomed treat nephrosis additionally as a spread of inflammatory and autoimmune diseases.

However, this parenterally administered drug fell out of favor when the greater clinical benefits of oral steroids were recognized. Its use is recently identified after Berg et al. observed reduction in proteinuria when ACTH was administered for lipid-lowering purpose in patients with IMN.
Initial experiences with ACTH are in Europe using ACTHtetracosactide, an artificial depot formulation. the info are conflicting. Several small case series reported reduction of proteinuria in IMN patients, many of whom were refractory to other therapies.

A little randomized control trial of 32 patients by Ponticelli et al. compared efficacy of 6 months of alkylating agents alternating with corticosteroids to tetracosactrin i.m injections for 1 year (1 milligram twice weekly). there have been no significant differences in cumulative remission rates. between the treatment arms initially (93% versus 87%, respectively) or at final follow-up of 21 months (75% total versus 87%, respectively). However, it's notable that these patients were treatment naïve, with preserved kidney function and low to modest degrees of proteinuria (5–6 g/d)—all of which can result in an excessively optimistic view of remission rates.

Outcomes weren't as favorable as in a very recent prospective study from Netherlands during which tetracosactrin was administered to high-risk IMN patients. Patients were considered at high risk for progression supported elevated urinary beta 2 microglobulin levels and high-grade proteinuria.

After 9 months of treatment, only 44% of patients achieved remission and relapse rates were high (43%). Other investigators have reported similarly high relapse rates after drug discontinuation, particularly after short courses of therapy a special formulation of ACTH, a natural highly purified gel, is obtainable within the us (corticotropin). during a retrospective study of corticotropin in proteinuric patients, 9 of 11 (82%) patients with IMN achieved a remission (3 complete; 6 partial). the entire remissions occurred in patients with relatively low levels of baseline proteinuria (2.6–4.8 g/d). Interpretations of the information are limited because of the uncontrolled nature of the study, the variable dosing regimens used, a possible carry-over effect from previously administered immunosuppression, and short follow-up. The mechanisms by which ACTH exerts its antiproteinuric effect aren't understood. Multiple mechanisms likely contribute and will involve both immune mediated and immune-independent mechanisms. the results aren't thought to be mediated by induction of endogenous cortisol from the adrenal glands because administration of corticosteroids as monotherapy has not been effective in IMN. However, it's conceivable that ACTH-induced increase in endogenous steroids might act differently than oral steroid preparations.

MATERIALS AND METHODS

Patients satisfying nephrotic syndrome criteria admitted to nephrology ward of TVMCH (i.e)

1. More than 3.5g/24hr urinary protein/ 1.73 m^2 BSA
2. Serum albumin<2.5g/dl
3. Clinical evidence of peripheral edema

METHOD OF COLLECTION OF STUDY

STUDY TYPE : Prospective cross sections study

AREA OF STUDY : Nephrology ward (I.P) and follow up of cases in OP

SAMPLE SIZE

80 Nephrotic syndrome cases admitted in TVMCH during the study period of December 1st 2018 to June 2020

STUDY DESIGN AND SAMPLING

All cases of nephrotic syndrome admitted in nephrology ward

INCLUSION CRITERIA

Adults age>18 years admitted with

1. Proteinuria (Nephrotic range)

   Urine PCR > 2 milligram/g

2. Raise RFT values

   Urea >40milligram/dl

Creatinine >1.2milligram/dl

EXCLUSION CRITERIA

1. Age less than 18 years
2. Pregnant females

METHODOLOGY

All patients diagnosed as nephrotic syndrome, detailed history, clinical examination and investigations with reference to renal abnormalities according to the proforma. The history includes facial puffiness, abdominal distension, pedal edema, hematuria, oliguria, symptoms of SLE, malignancy, jaundice, anorexia, loss of weight and loss of apetite, past history, treatment history and associated comorbid conditions. Detailed physical examination was done. The investigations included complete blood count, renal & liver function test, complete urine analysis, 24 hours urine protein excretion and renal biopsy. After consent from the patient, under sterile aseptic precautions, local anesthesia (2% lignocaine) was given, using 18 G needle renal biopsy was done, usually left kidney is preferred 2 samples were taken, one from the cortex and the other from cortico-medullary junction for immunohistology and electron microscopy. The samples were sent to pathology lab with formalin & michels fixative respectively. Michel's fixatives is for immune florescence which is stained for PLA2R, IgG, IgM, C3, C1q, Kappa & lambda light chains. PAS, silver & trichrome staining were also done for light microscopy.

OBSERVATION AND RESULTS

TABLE 1 : Age distribution of nephrotic syndrome cases in adults

AGE GROUP	FREQUENCY	PERCENT
< 20	9	11.3
21-30	14	17.5
31-40	19	23.8
41-50	20	25.0
51-60	10	12.5
>61	8	10.0
TOTAL	80	100.0

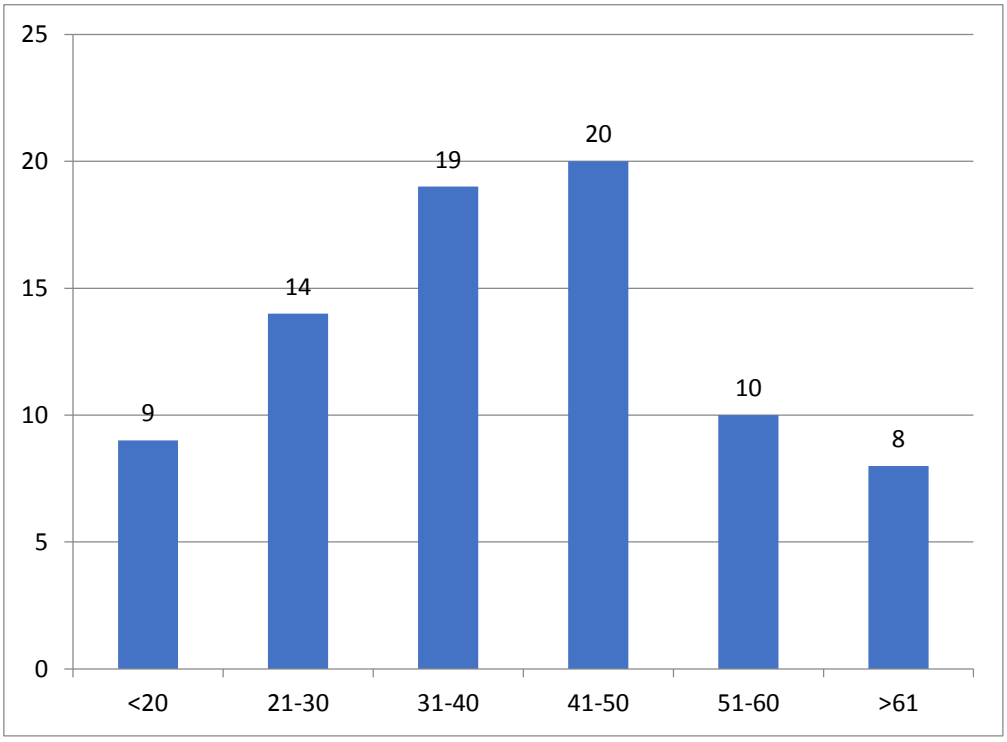


TABLE 2 : Sex distribution of nephrotic syndrome cases in adults

SEX	SEX DISTRIBUTION	PERCENT
FEMALE	45	56.3
MALE	35	43.8
TOTAL	80	100.0

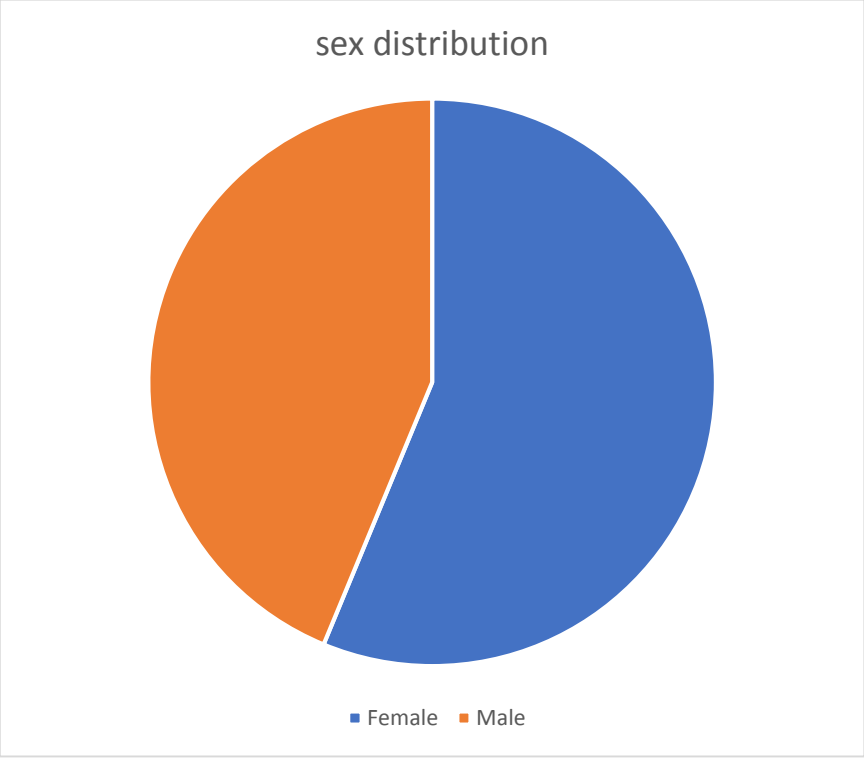


TABLE 3: Causes of nephrotic syndrome in adults

Biopsy Report	Frequency	Percent
Amyloidosis	3	3.8
Diabetic Nephropathy	10	12.5
Diffuse Lupus Nephritis	5	6.3
FSGS	10	12.5
primary MN PLA2R -ve	3	3.8
secondary MN PLA2R -ve	5	6.3
primary MN PLA2R +ve	20	25.0
Minimal change Glomerulopathy	10	8.0
MPGN	7	8.8
Myeloma kidney	1	1.3
RPGN	6	7.5
Total	80	100.0

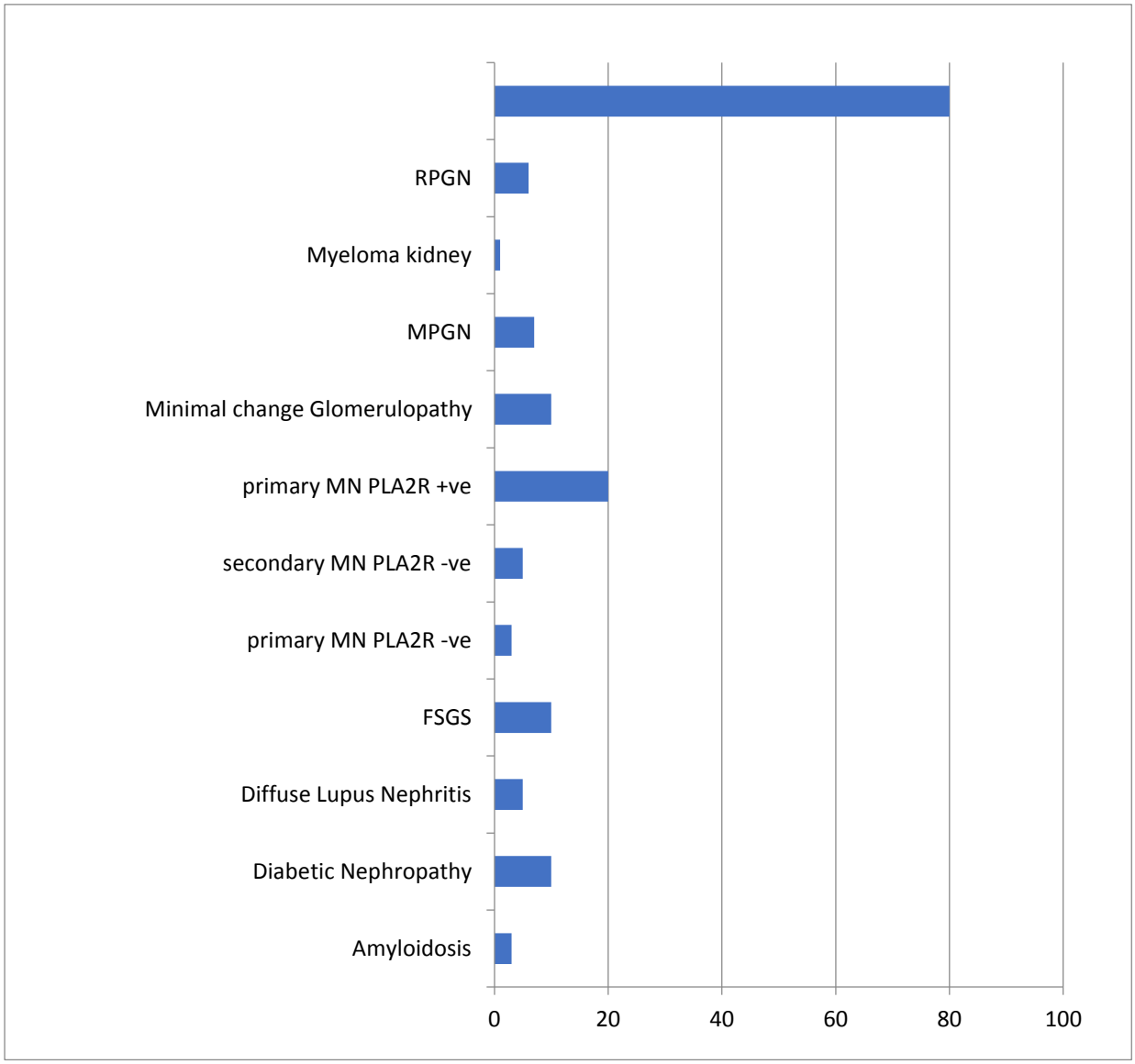

RPGN
Myeloma kidney
MPGN
Minimal change Glomerulopathy
primary MN PLA2R +ve
secondary MN PLA2R -ve
primary MN PLA2R -ve
FSGS
Diffuse Lupus Nephritis
Diabetic Nephropathy
Amyloidosis
0
20
40
60
80
100

TABLE 4: Sensitivity and specificity of PLA2R in identifying primary MN cases

PLA2R STATUS	BIOPSY REPORT		TOTAL	P VALUE
	PRIMARY MN	SECONDARY MN		
Positive	20	0	20	<0.0001
Negative	3	5	8	
Total	23	5	28	

From the above table,

SENSITIVITY OF PLA2R TEST = True positive

True Positive + False Negative

= 20/ (20+3) = **86.9%**

SPECIFICITY OF PLA2R TEST = True Negative

True Negative + False positive

= 5/ (0+5) = **100%**

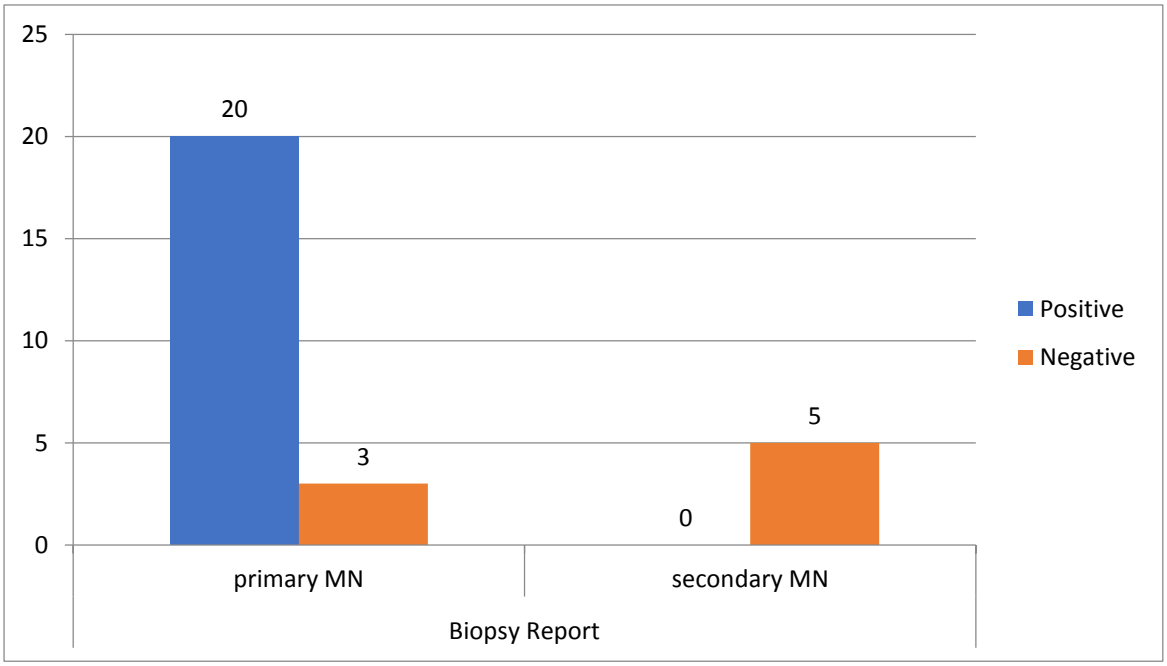

25
20
15
10
5
0
20
3
0
5
primary MN
secondary MN
Biopsy Report
Positive
Negative

TABLE 5**: Age distribution of membranous nephropathy cases in adults**

Age group	Frequency	Percent
<40	5	21.7
41-50	10	43.5
51-60	6	26.1
>61	2	8.7
Total	23	100.0

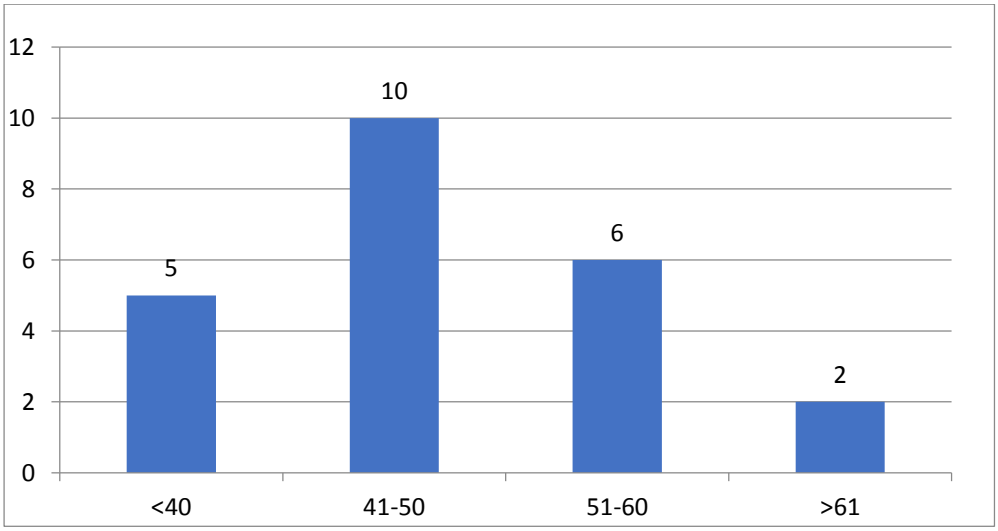


TABLE 6: **: Sex distribution of membranous nephropathy cases in adults**

Gender	Frequency	Percent
F	7	30.4
M	16	69.6
Total	23	100.0

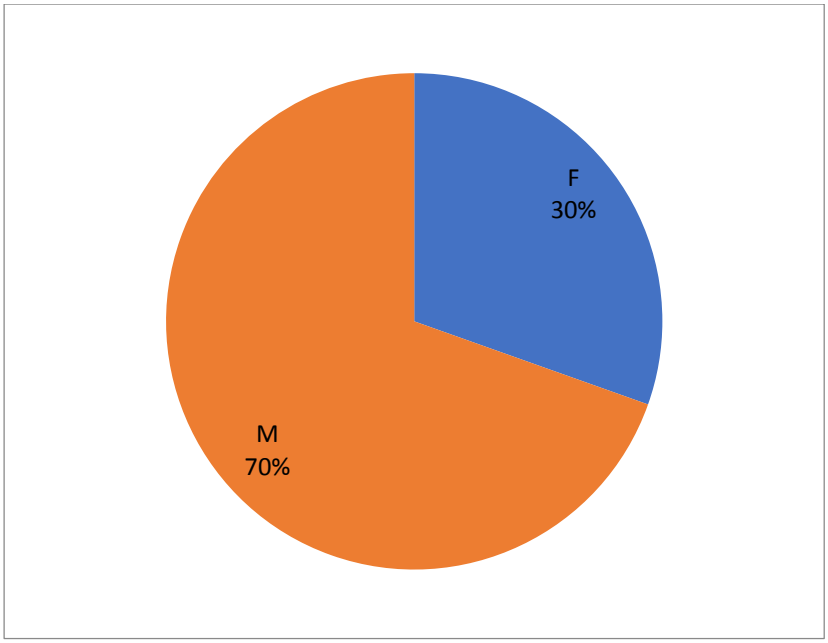
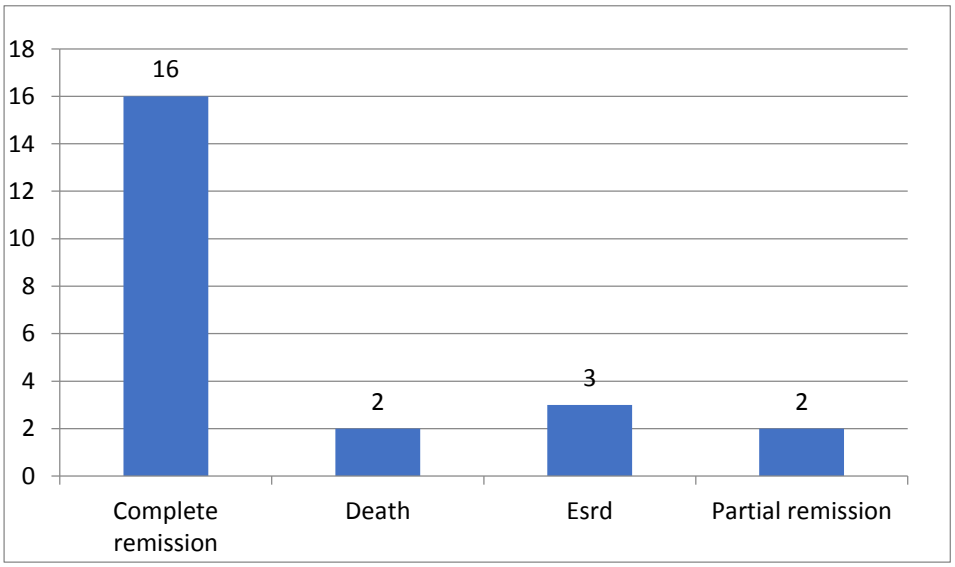


TABLE 7: End point of IMN patients treated with modified Ponticelli regimen for six months

End point	Frequency	Percent
Complete remission	16	69.6
Death	2	8.7
Esrd	3	13.0
Partial remission	2	8.7
Total	23	100.0



DISCUSSION

We conducted a prospective observational study of 80 nephrotic syndrome patients admitted in the department of nephrology, TVMCH during the period of December 1st 2018 to June 2020 out of the eighty patients 28 patients had membranous nephropathy, 10 patients had diabetic nephropathy , 10 pateints had minimal change nephropathy, 10 patients had FSGS, 7 patients had MPGN, 6 patients had RPGN, 5 patients had lupus nephritis , 3 patients had amyloidosis and 1 patient had myeloma kidney in their biopsy report. Membranous nephropathy was the most common among the 80 patients and the second common being diabetic nephropathy , minimal change nephropathy and FSGS

Of the 28 pateints of membranous nephropathy staining for PLA2R was done by immunofluoroscence technique. Age of presentation of membranous nephropathy was between 30 and 70 , with most of the cases between 40 and 60. Males were twice affected than females. Only patients with nephrotic syndrome and renal failure was taken for the study. 20 patients were PLA2R positive hence they were classified as Idiopathic membranous nephropathy. 8 patients were PLA2R negative. Of the 8 patients, 5 patients had an identifiable cause . Two patients has SLE ,one patient had hepatitis B, one had hepatitis C and one patient had colon cancer who died during follow up period due to liver metastases. Those five patients were classified as secondary membranous nephropathy and treatment were given for their underlying cause. Out of the 8 patients who were

PLA2R negative underlying cause couldn't be identified for 3 cases though a thorough search was made for autoimmune disease, malignancy, infections , drug history was also ruled out they were classified as PLA2R negative primary membranous nephropathy.

Out of the 80 study cases 23 patients had idiopathic membranous nephropathy. These 23 patients were treated with modified Ponticelli regimen as they had both nephrotic syndrome and renal failure . Intravenous methylprednisolone(1milligram/kg body weight per day) followed by oral prednisolone was given for months 1 , 3 and 6 .Oral cyclophosphamide 2milligram/kg/day was given for 30 days in months 2 , 4 and 6 . The treatment end point of the patients after six months was as follows :

1. 16 patients had complete remission of proteinuria and renal failure. The daily urinary protein became less than 150 milligram and the urea and creatinine values returned to baseline.
2. 2 patients had partial remission of proteinuria and renal failure.
3. 3 patients progressed to ESRD who required dialysis and they are on maintenance hemodialysis.
4. 2 patients died during follow up due to complications of renal failure. These 2 patients had stage 4 disease in biopsy with rapidly progressing renal failure.

The sensitivity of PLA2R test in our study was 86.9 percent and specificity being 100 percent . The p value is less than 0.0001 which is statistically significant.

The complete remission of the disease after using modified ponticelli regimen is 69.56% which is non inferior to newer regimens containing MMF(remission rate of 70%) and calcineurin inhibitors (50% at 6months and 80% in one year).

CONCLUSION

1. From our study, the most common cause of nephrotic syndrome in adults is membranous nephropathy (35% among adult nephrotic syndrome patients). Males are twice affected than females (2:1)
2. Primary membranous nephropathy is more common than secondary membranous nephropathy. 82% of the membranous nephropathy cases were primary.
3. The sensitivity of PLA_2R is 86.9% and specificity is 100% in identifying primary membranous nephropathy. Due to its 100% specificity ruling out the innumerable secondary causes is not routinely required if PLA2R is positive in biopsy.
4. The modified Ponticelli regimen has a complete remission rate of 69.6% which is non-inferior to newer regimens containing Mycofenolate Mofetil (remission rate – 70%) and calcineurin inhibitors (50% at 6 months and 80% in one year)022

RECOMMENDATIONS

1. PLA2R immunofluroscence can be done in all biopsy specimens which are positive for membranous Nephropathy.
2. We can use low dose steroids and cyclophosphamide in achieving remission in idiopathic membranous nephropathy.
3. ANA should be done in all young female cases presenting with membranous nephropathy and a thorough search for malignancy must be done for all old age patients with membranous nephropathy if PLA2R immunofluroscence is negative in biopsy.

LIMITATIONS

1. The study population is very low. Large randomised multi centric trials are required to compare the efficacy of modified Ponticelli regimen with other regimens used in idiopathic membranous nephropathy.

2. Long term follow up is required to know about the relapse rate after remission with modified Ponticelli regimen.

BIBLIOGRAPHY

1. Ponticelli C., Glassock R.J. Glomerular diseases: membranousnephropathy–a modern view. Clin J Am Soc Nephrol. 2014;9:609–616

2. Polanco N., Gutiérrez E., Covarsí A. Grupo de Estudio de las Enfermedades Glomerulares de la Sociedad Española de Nefrología. Spontaneous remission of nephrotic syndrome in idiopathic membranous nephropathy. J Am Soc Nephrol. 2010;21:697–704

3. Schieppati A., Mosconi L., Perna A. Prognosis of untreated patients with primary membranous nephropathy. N Engl J Med. 1993;329:85–89.

4. Beck L.H., Bonegio R.G.B., Lambeau G. M-type phospholipase A2 receptor as target antigen in primary membranous nephropathy. N Engl J Med. 2009;361:11–21.

5. Tomas N.M., Beck L.H., Jr., Meyer-Schwesinger C. Thrombospondin type-1 domain-containing 7A in idiopathic membranous nephropathy. N Engl J Med. 2014;371:2277–2287

6. Hofstra J.M., Beck L.H., Beck D.M. Anti-phospholipase A_2 receptor antibodies correlate with clinical status in primary membranous nephropathy. Clin J Am Soc Nephrol. 2011;6:1286–1291.

7. Hoxha E., Thiele I., Zahner G. Phospholipase A2 receptor autoantibodies and clinical outcome in patients with primary membranous nephropathy. J Am Soc Nephrol. 2014;25:1357–1366

8. Hoxha E., Harendza S., Pinnschmidt H. PLA2R antibody levels and clinical outcome in patients with membranous nephropathy and nonnephrotic range proteinuria under treatment with inhibitors of the renin-angiotensin system. PLoS One. 2014;9

9. Kim Y.G., Choi Y.W., Kim S.Y. Anti-phospholipase A2 receptor antibody as prognostic indicator in idiopathic membranous nephropathy. Am J Nephrol. 2015;42:250–257

10. Dahan K., Debiec H., Plaisier E. Rituximab for severe membranous nephropathy: a 6-month trial with extended follow-up. J Am Soc Nephrol. 2017;28:348–358

11. Ruggenenti P., Debiec H., Ruggiero B. Antiphospholipase A2 receptor antibody titer predicts post-rituximab outcome of membranous nephropathy. J Am Soc Nephrol. 2015;26:2545–2558.

12. Remuzzi G., Chiurchiu C., Abbate M. Rituximab for idiopathic membranous nephropathy. Lancet. 2002;360:923–924.

13. Fervenza F.C., Cosio F.G., Erickson S.B. Rituximab treatment of idiopathic membranous nephropathy. Kidney Int. 2008;73:117–125.

14. Cravedi P., Sghirlanzoni M.C., Marasà M. Efficacy and safety of rituximab second-line therapy for membranous nephropathy: a prospective, matched-cohort study. Am J Nephrol. 2011;33:461–468

15. Beck L.H., Jr., Fervenza F.C., Beck D.M. Rituximab-induced depletion of anti-PLA2R autoantibodies predicts response in membranous nephropathy. J Am Soc Nephrol. 2011;22:1543–1550.

16. Cravedi P., Ruggenenti P., Sghirlanzoni M.C. Titrating rituximab to circulating B cells to optimize lymphocytolytic therapy in idiopathic membranous nephropathy. Clin J Am Soc Nephrol. 2007;2:932–937

17. Bech A.P., Hofstra J.M., Brenchley P.E. Association of anti-PLA_2R antibodies with outcomes after immunosuppressive therapy in idiopathic membranous nephropathy. Clin J Am Soc Nephrol. 2014;9:1386–1392

18. De Vriese A., Glassock R., Nath K. A proposal for a serology-based approach to membranous nephropathy. J Am Soc Nephrol. 2017;28:421–430

19. Dähnrich C., Komorowski L., Probst C. Development of a standardized ELISA for the determination of autoantibodies against human M-type phospholipase A2 receptor in primary membranous nephropathy. Clin Chim Acta. 2013;421:213–218.

20. Rojas-Rivera J., Fernández-Juárez G., Ortiz A. European multicentre and open-label controlled randomized trial to evaluate the efficacy of sequential treatment with tacrolimus-rituximab versus steroids plus cyclophosphamide in patients with primary membranous nephropathy: the STARMEN study. Clin Kidney J. 2015;8:503–510

21. Waldman M., Beck L.H., Jr., Braun M. Membranous nephropathy: pilot study of a novel regimen combining cyclosporine and rituximab. Kidney Int Rep. 2016;1:73–84.

ANNEXURE

PROFORMA

Name: OP. No: IP No:

Age: Male/Female Occupation:

Date of First visit:

Address:

History (in chronological order)

Tick the symptoms present

Pedal edema	Alopecia	Arthralgia
Abdominal distension	Oral ulcers	Myalgia
Facial puffiness	Rashes	Jaundice
Hematuria	Photosensitivity	Anorexia
Oliguria	Fever	Weight loss

Past History:

Diabetes :

Previous similar episodes:

Hypertension :

Known renal disease :

Drug history:

NSAIDS, Steroids, cyclophosphamide, Azathioprine, methotrexate

EXAMINATION:

Height	Weight	BSA	Pallor	Cyanosis
Clubbing	Lymphedenopits	Pulse	BP	Respiratory rate
Temp	Skin	Edema	Facial puffiness	
Chart & CVS				
Abdomen				
CNS				
Musculo skeletal				

INVESTIGATION:

Hb:	TC:	DC:	ESR:	Platelet count:
Urea:	Creatinine:			
TB:	DB:	SGO1:	SGPS:	ACP:
FBS:	PPBS:			
HbSAg:	HCV:	ANA:		
Urine albumin:				
Sugar:				
Urine Spot PCR:				

24 hour urinary protein:				
CXR:	ECG:			
Renal Biopsy:				

சிறுநீரக திசு பரிசோதனை ஒப்புதல் படிவம்

நான் எனக்கு / எனது _____ க்கு சிறுநீரக நோய் இருப்பதால் உடல் முழுவதும் நீர் கோர்த்துள்ளது மற்றும் சிறுநீரக செயல்பாடு பாதிக்கப்பட்டுள்ளது என்பதை மருத்துவர் மூலம் தெரிந்து கொள்கின்றேன். அந்த சிறுநீரக நோயின் காரணத்தை தெரிந்து கொள்ளவும் மேலும் உரிய மருந்து செலுத்தவும் சிறுநீரக திசு பரிசோதனை அவசியம் என்பதை தெரிந்துகொண்டேன். திசு பரிசோதனையின் வழிமுறையையும் அதன் பக்கவிளைவுகளையும் மருத்துவரின் மூலம் அறிந்தபின் நான் எனக்கு/எனது _____ சிறுநீரக திசு பரிசோதனை செய்து கொள்ள சம்மதிக்கிறேன்.

நோயாளியின் பெயர்: _____ தேதி:

நோயளியின் உறவினர் பெயர்: _____ இடம்:

கையொப்பம்: _____

நோயாளிகளுக்கு அறிவிப்பு மற்றும் ஒப்புதல் படிவம்
(மருத்துவ ஆய்வில் பங்கேற்பதற்கு)

ஆய்வு செய்யப்படும் தலைப்பு:
பங்கு பெறுவரின் பெயர்:
பங்கு பெறுவரின் வயது:

		பங்கு பெறுவர் இதனை ✓ குறிக்கவும்
1.	நான் மேலே குறிப்பிட்டுள்ள மருத்துவ ஆய்வின் விவரங்களை படித்து புரிந்து கொண்டேன். என்னுடைய சந்தேகங்களை கேட்கவும், அதற்கான தகுந்த விளக்கங்களை பெறவும் வாய்ப்பளிக்கப்பட்டுள்ளது என அறிந்து கொண்டேன்.	
2.	நான் இவ்வாய்வில் தன்னிச்சையாக தான் பங்கேற்கிறேன். எந்த காரணத்தினாலோ எந்த கட்டத்திலும், எந்த சட்ட சிக்கலுக்கும் உட்படாமல் நான் இவ்வாய்வில் இருந்து விலகி கொள்ளலாம் என்றும் அறிந்து கொண்டேன்.	
3.	இந்த ஆய்வு சம்பந்தமாகவோ, இதை சார்ந்து மேலும் ஆய்வு மேற்காள்ளும் போதும் இந்த ஆய்வில் பங்குபெறும் மருத்துவர் என்னுடைய மருத்துவ அறிக்கைகளை பார்ப்பதற்கு என் அனுமதி தேவையில்லை என அறிந்து கொள்கிறேன். நான் ஆய்வில் இருந்து விலகிக் கொண்டாலும் இது பொருந்தும் என அறிகிறேன்.	
4.	இந்த ஆய்வின் மூலம் கிடைக்கும் தகவலையோ, முடிவையோ பயன்படுத்திக் கொள்ள மறுக்க மாட்டேன்.	
5.	இந்த ஆய்வில் பங்கு கொள்ள ஒப்புக் கொள்கிறேன் எனக்கு கொடுக்கப்பட்டஅறிவுரைகளின் படி நடந்து கொள்வதுடன், ஆய்வை மேற்கொள்ளும் மருத்துவ அணிக்கு உண்மையுடன் இருப்பேன் என்று உறுதியளிக்கிறேன். என் உடல் நலம் பாதிக்கப்பட்டாலோ, அல்லது எதிர்பாராத, வழக்கத்திற்கு மாறான நோய்குறி தென்பட்டாலோ உடனே இதை மருத்துவ அணியிடம் தெரிவிப்பேன் என உறுதி அளிக்றேன்.	

பங்கேற்பவரின் கையொப்பம் / ..... இடம் .....
கட்டைவிரல் ரேகை
பங்கேற்பவரின் பெயர் மற்றும் விலாசம் .....
ஆய்வாளரின் கையொப்பம் /..... இடம் .....
ஆய்வாளரின் பெயர் .....
மையம் .....
கல்வியறிவு இல்லாதவற்கு (கைரேகை வைத்தவர்களுக்கு) இது அவசியம் தேவை
சாட்சியின் கையொப்பம் /..... இடம் .....
பெயர் மற்றும் விலாசம் ....

S.No	Name	Age	Age group	Sex	Urea	Creatinine	Urine Albumin	Urine Sugar	Urine PCR	24 hr/Urinary Protein	ANA	HBsAg	HCV	FBS	PPBS	Biopsy Report
1	Madhabala	16	1	F	40	1.2	++++	Nil	4.2	5.8	negative	negative	negative	105	140	Minimal Change Glomerulopathy
2	Madavi	18	1	F	41	1.4	++++	–	3	4.5	negative	negative	negative	70	130	Minimal Change Glomerulopathy
3	Nagajothi	18	1	F	39	2.9	+++	–	1.9	3.5	negative	negative	negative	78	130	FSGS
4	Karpagavalli	19	1	F	48	2.9	+++	–	3.5	4.6	positive	negative	negative	105	140	MPGN
5	Arul Jeba Raj	19	1	M	40	1.3	++++	–	3.8	5.6	negative	negative	negative	90	128	Minimal Change glomerulopathy
6	Arumugam	20	1	M	105	9.2	+++	Nil	1.9	3.8	negative	negative	negative	70	128	RPGN
7	Jeya Shree	20	1	F	95	1.3	++++	–	3	4.5	negative	negative	negative	65	138	Minimal Change Glomerulopathy
8	Manikandan	20	1	M	55	2.5	++++	–	1.7	3.8	negative	negative	negative	75	131	FSGS
9	Muthupandi	20	1	M	45	1.3	++++	–	2.8	4.2	negative	negative	negative	65	121	Minimal change Glomerulopathy
10	Balaganesh	21	2	M	40	1.1	++++	Nil	1.5	3.8g	negative	negative	negative	70	109	Minimal Change Glomerulopathy
11	Anitha	21	2	F	48	3.9	+++	–	3.8	3.6	positive	negative	negative	78	129	Diffuse Lupus Nephritis
12	Priya	22	2	F	78	3.5	+++	–	1.8	3.6	negative	negative	negative	95	110	Diffuse Lupus Nephritis
13	Esakkiammal	23	2	F	78	4.1	+++	–	2.5	4.9	negative	negative	negative	76	135	FSGS
14	Ashok	24	2	M	49	2.5	+++	Nil	1.9	3.8	negative	negative	positive	105	139	Membranous Nephropathy PLA2R negative (secondary)
15	Muthuselvi	25	2	F	78	4.1	++++	–	3.2	4.8	positive	negative	negative	90	125	Diffuse Lupus Nephritis
16	Duraichi	26	2	F	98	4.1	+++	–	3.9	4.6	negative	negative	negative	78	136	FSGS
17	Gomuthai	26	2	F	68	6.8	+++	–	2.5	3.8	positive	negative	negative	81	119	Diffuse Lupus Nephritis
18	Mohamed Ayub khan	27	2	M	48	1.5	++++	–	1.5	3.7	negative	negative	negative	75	119	Minimal change Glomerulopathy
19	Muthumari	27	2	F	71	1.8	++++	–	2.5	3.5	negative	negative	negative	70	105	FSGS
20	Madha murugan	28	2	F	39	2.5	+++	–	1.9	3.8	positive	negative	negative			Membranous Nephropathy PLA2R negative (secondary)
21	Manikandan	28	2	F	95	38	++++	–	3.9	4.2	negative	positive	negative	91	130	MPGN
22	Amutha	28	2	F	128	10.2	++++	–	5.2	6.9	negative	negative	negative	78	135	RPGN
23	Michael Antony	28	2	M	98	7.5	+++	–	1.8	3.5	negative	negative	negative	80	128	RPGN
24	Kala	32	3	F	58	3.1	++++	–	3.5	4.1	negative	negative	negative	80	118	MPGN
25	Kannan	32	3	M	72	4.2	+++	–	2.9	4.6	negative	negative	negative	89	125	MPGN
26	Kovil Raj	33	3	M	65	2.1	++++	–	2.8	4	negative	negative	negative	80	128	FSGS
27	Poomari	34	3	F	78	2.1	+++	–	1.5	3.9	negative	negative	negative	80	114	MPGN
28	Johnson	35	3	M	99	6.2	+++	Nil	1.5	4.9	negative	negative	negative	105	138	RPGN
29	Moorthy	35	3	M	45	1.3	++++	–	1.9	3.6	negative	negative	negative	65	98	Minimal Change glomerulopathy
30	Amma Ponnu	36	3	F	35	1	+++	Nil	1.5	4.1	negative	negative	negative	95	118	Minimal change nephropathy
31	Gomathi	36	3	F	68	3.8	+++	–	2.5	3.8	positive	negative	negative	81	119	Diffuse Lupus Nephritis
32	Radha	36	3	F	70	1.9	+++	–	2.8	4	negative	negative	negative	80	105	Minimal change Glomerulopathy
33	Balasubramanian	37	3	M	91	4.1	+++	Nil	1.9	4.1	negative	negative	negative	90	138	Membranous Nephropathy PLA2R negative (primary)
34	Gowry	37	3	F	109	9.8	+++	–	3.2	5.6	negative	negative	negative	78	125	RPGN
35	Jancy	37	3	F	69	2.5	++++	–	1.9	3.5	negative	negative	negative	75	128	FSGS
36	Manthira Moorthy	37	3	M	42	1.2	++++	–	1.9	3.6	negative	negative	negative	60	105	Membranous Nephropathy PLA2R postive (primary)
37	Raja Manickam	37	3	M	75	2.5	+++	–	1.2	3.5	negative	negative	negative	78	108	MPGN
38	Esakkiammal	38	3	F	91	1.9	+++	++	3.1	5.2	negative	negative	negative	138	294	Diabetic Nephropathy
39	Jeya	38	3	F	95	8.5	++++	–	2.8	3.9	negative	negative	negative	62	128	RPGN
40	Maheshwari	38	3	F	65	1.9	++++	–	2.5	4.6	negative	negative	negative	98	128	Membranous Nephropathy PLA2R negative (primary)
41	Pappa Ebenezar	40	3	F	45	1.2	+++	–	1.9	3.6	negative	negative	negative	105	149	Membranous Nephropathy PLA2R postive (primary)
42	Mathi Arasan	40	3	M	105	5.8	++++	–	3.8	6.2	negative	negative	negative	68	128	Membranous Nephropathy PLA2R postive (primary)
43	Alif laila	41	4	F	42	1.8	++++	++	2.5	3.7	negative	negative	negative	110	235	Diabetic Nephropathy

S.No	Name	Age	Age group	Sex	Urea	Creatinine	Urine Albumin	Urine Sugar	Urine PCR	24 hr/Urinary Protein	ANA	HBsAg	HCV	FBS	PPBS	Biopsy Report
44	Kannan	41	4	M	48	3.2	++++	–	2.5	3.9	negative	negative	negative	100	138	Membranous Nephropathy PLA2R postive (primary)
45	Krishnan	41	4	M	65	2.3	+++	–	2	3.5	negative	negative	negative	70	116	FSGS
46	Muthupalaveam	41	4	M	45	1.3	++++	–	2.9	5.6	negative	negative	negative	80	132	Membranous Nephropathy PLA2R postive (primary)
47	Jeyakumar	42	4	M	95	4.8	+++	Nil	1.2	3.1	negative	negative	negative	95	125	Amyloidosis
48	Jeganathan	42	4	M	55	4.1	+++	–	2.8	4.9	negative	negative	negative	85	115	Membranous Nephropathy PLA2R postive (primary)
49	Kumar	42	4	M	48	1.4	++++	–	3.9	5.1	negative	negative	negative	68	125	Membranous Nephropathy PLA2R postive (primary)
50	Mallika	42	4	F	50	1.5	+++	–	2.9	5.3	negative	negative	negative	65	120	Membranous Nephropathy PLA2R postive (primary)
51	Aslin Bindhu	43	4	F	45	3.2	+++	Nil	1.9	3.6	positive	negative	negative	105	135	Membranous Nephropathy PLA2R negative (secondary)
52	Akila	43	4	F	105	6.3	++++	–	6.9	5.5	negative	negative	negative	105	128	Membranous Nephropathy PLA2R postive (primary)
53	Alagammal	45	4	F	42	2.3	+++	nil	2.5	3.6	negative	negative	negative	75	102	Membranous Nephropathy PLA2R postive (primary)
54	Mary	45	4	F	48	1.3	+++	–	1.4	3.6	negative	negative	negative	70	125	Membranous Nephropathy PLA2R postive (primary)
55	Muppidathi	45	4	F	58	2.1	++++	–	2.1	3.7	negative	negative	negative	120	198	Diabetic Nephropathy
56	Jeyanthi	46	4	F	40	1.2	+++	–	1.9	3.8	negative	negative	negative	105	165	Diabetic Nephropathy
57	Pauldurai	46	4	F	87	2.1	++++	–	3	4.1	negative	negative	negative	105	198	Diabetic Nephropathy
58	Chellammal	47	4	F	48	2.8	+++	++	1.8	3.7	negative	negative	negative	140	320	Diabetic Nephropathy
59	Iyyappan	48	4	M	120	5.6	+++	–	3.1	4.9	negative	negative	negative	68	108	Membranous Nephropathy PLA2R postive (primary)
60	Lakshmi	50	4	F	60	2.5	+++	–	1.5	3.4	negative	negative	negative	120	265	Diabetic Nephropathy
61	Pathirakali	50	4	F	45	1.3	+++	–	2.8	4.9	negative	negative	negative	90	135	Diabetic Nephropathy
62	Ramachandran	50	4	M	41	1.3	+++	–	2.9	4.1	negative	negative	negative	105	138	Membranous Nephropathy PLA2R postive (primary)
63	Bowsiya	52	5	F	105	5.9	+++	Nil	2.5	4.5g	negative	negative	negative	91	130	MPGN
64	Elakiya Siva	52	5	M	60	2.5	++++	Nil	2.5	3.6g	negative	negative	negative	99	128	Membranous Nephropathy PLA2R postive (primary)
65	Adaikalam	52	5	M	95	6.9	+++	–	2.5	5	negative	negative	negative	105	169	Membranous Nephropathy PLA2R postive (primary)
66	Kulasekaram	52	5	M	60	1.4	++++	–	1.9	3.6	negative	negative	negative	70	130	Membranous Nephropathy PLA2R postive (primary)
67	Nataraja	52	5	M	45	1.4	++++	–	2.3	4.9	negative	negative	negative	85	138	Membranous Nephropathy PLA2R postive (primary)
68	Fathima Beevi	54	5	F	42	2.5	+++	–	1.5	3.6	negative	negative	negative	128	195	Diabetic Nephropathy
69	Nellaiappan	54	5	M	98	1.2	+++	–	2.8	5	negative	negative	negative	85	135	Membranous Nephropathy PLA2R postive (primary)
70	Eswari	55	5	F	118	5.9	+++	Nil	2.3	3.1	negative	negative	negative	105	148	FSGS
71	Ganesan	55	5	M	58	2.9	+++	–	1.2	3.6	negative	negative	positive	70	128	Membranous Nephropathy PLA2R negative (secondary)
72	Magalingam	56	5	M	49	1.3	++++	–	2.8	4	negative	negative	negative	68	115	Membranous Nephropathy PLA2R postive (primary)
73	Kovil Pitchai	62	6	M	108	7.9	+++	–	32	5.8	negative	negative	negative	98	125	Membranous Nephropathy PLA2R postive (primary)

S.No	Name	Age	Age group	Sex	Urea	Creatinine	Urine Albumin	Urine Sugar	Urine PCR	24 hr/Urinary Protein	ANA	HBsAg	HCV	FBS	PPBS	Biopsy Report
74	Malaiyammal	66	6	F	68	2.1	+++	Nil	1.7	3.6	negative	negative	negative	81	129	Membranous Nephropathy PLA2R negative (primary)
75	Madasamy	68	6	M	40	1.3	+++	++	1.9	3.6	negative	negative	negative	148	301	Diabetic Nephropathy
76	Prema Kala	68	6	F	58	2.8	++++	—	1.8	3.5	negative	negative	negative	115	285	Myeloma kidney
77	Balamurugan	70	6	M	95	5.2	+++	—	1.9	3.6	negative	negative	negative	105	138	Amyloidosis
78	Jaswa Smilson	76	6	M	79	3.8	+++	—	2.8	4.1	negative	negative	negative	105	139	Membranous Nephropathy PLA2R negative (secondary)
79	Malar	79	6	F	91	3.6	+++	—	2.8	3.6	negative	negative	negative	79	145	FSGS
80	Mariammal	80	6	F	78	5.2	++++	—	1.2	3.5	negative	negative	negative	69	135	Amyloidosis

S.No	Name	Age	Sex	At Presentation					3 months of Treatment					6 months of Treatment							
				Urea	Creatinine	Urine Albumin	Urine PCR	24 hr/Urinary Protein	Urea	Creatinine	Urine Albumin	Urine PCR	24 hr/Urinary Protein	Urea	Creatinine	Urine Albumin	Urine PCR	24 hr/Urinary Protein	PLA2R status	End point	Biopsy Report
1	Balasubramanian	37	M	91	4.1	†††	1.9	4.1	71	3	††	1.5	3	65	2.8	†	1	2.5	Negative	Esrd	**Diabetic Nephropathy**
2	Manthira Moorthy	37	M	42	1.2	††††	1.9	3.6	30	0.9	Trace	0.2	0.35	28	0.6	Nil	0.1	0.14	Positive	Complete remission	**Membranous Nephropahty PLA2R negative(primary)**
3	Maheshwai	38	F	65	1.9	††††	2.5	4.6	60	1.7	†††	1.9	3.1	55	1.5	†	1	2	Negative	Partial remission	**Membranous NephropathyPLA2-ve (secondary)**
4	Pappa Ebenezar	40	F	30	0.7	†††	1.9	3.6	30	0.7	Trace	0.18	0.22	20	0.5	Nil	0.09	0.15	Positive	Complete remission	**Membranous Nephropathy PLA2R negative(primary)**
5	Mathi	40	M	105	5.8	††††	3.8	6.2	68	5	††	1.8	3.1	51	4.5	†	0.5	0.8	Positive	Complete remission	**Minimal change glomerucopathy**
6	Kannan	41	M	48	3.2	††††	2.5	3.9	35	1	Trace	0.2	18	18	0.5	Nil	0.11		Positive	Complete remission	**Membranous Nephropathy PLA2 negative(secondary)**
7	Muthupalavesam	41	M	45	1.3	††††	2.9	5.6	30	0.9	Trace	0.3	5.6	25	0.7	Nil	0.1	0.1	Positive	Complete remission	**Membranous Nephropathy PLA2R positive(primary)**
8	Jeganathan	42	M	78	5.6	†††	2.8	4.9	55	4.1	††	0.5	1.1	60	2.5	—	0.1	0.2	Positive	Esrd	**Amyloidosis**
9	Kumar	42	M	48	1.9	††††	3.9	5.1	40	0.8	Trace	0.3	1	31	0.8	Nil	0.08	0.25	Positive	Complete remission	**MPGN**
10	Mallika	42	F	50	1.5	†††	2.9	5.3	45	0.9	—	1	2.6	30	0.7	Nil	0.2	0.2	Positive	Complete remission	**Minimal Change Glomerulopathy**
11	Akila	43	F	105	6.3	††††	6.9	5.5	120	7.8	Pt died due to Pulm edema								Positive	Death	**Membranous Nephropathy PLA2R positive(primary)**
12	Alagammal	45	F	42	2.3	†††	2.5	3.6	40	1.8	†	1	1.5	30	1	—	0.15	0.2	Positive	Complete remission	**Membranous Nephropathy PLA2 postive (primary)**
13	Mary	45	F	48	1.3	†††	1.4	3.6	30	1	Trace	0.9	1.5	25	0.7	Nil	0.1	0.1	Positive	Complete remission	**FSGS**
14	Iyyappan	48	M	120	5.6	††††	3.2	4.9	70	4.9	††	1.5	1.9	50	3.5	Trace	0.2	0.5	Positive	esrd	**FSGS**
15	Ramachandran	50	M	41	1.3	††††	2.9	4.1	30	1	Trace	0.1	4.1	19	0.6	Nil	0.05	0.25	Positive	Complete remission	**Diabetic Nephropathy**
16	Elakiya Siva	52	M	60	2.5	††††	2.5	3.6	42	1.8	†	1	1	25	0.9	Nil	0.2	0.1	Positive	Complete remission	**Minimal change nephropathy**
17	Adaikalam	52	M	95	6.9	†††	2.5	5	68	4.5	†	0.9	1.1	40	3.5	Trace	0.2	0.3	Positive	Complete remission	**MPGN**
18	Kulasekaran	52	M	60	1.4	††††	1.9	3.6	35	0.9	Trace	0.3	0.3	25	0.5	—	0.11	0.15	Positive	Complete remission	**Membranous Nephropathy PLA2 R positive(primary)**
19	Nataraja	52	M	45	1.4	††††	2.3	4.9	30	0.9	Trace	0.2	0.4	28	0.7	Nil	0.1	0.1	Positive	Complete remission	**Membranous Nephropahty PLA2R positive(primary)**
20	Nellaiappan	54	M	98	1.2	†††	2.8	5	28	0.8	Nil	0.1	0.25	18	0.6	Nil	0.1	0.5	Positive	Complete remission	**MPGN**
21	Magalingam	56	M	49	1.3	††††	2.8	4	30	0.6	Nil	0.1	18	18	0.7	0.15	0.11		Positive	Complete remission	**Diabetic Nephropathy**
22	Kovil Pitchai	62	M	108	7.9	†††	3.2	5.8	pt died due to renal failure										Positive	Death	**RPGN**
23	Malaiyammal	66	F	68	2.1	†††	1.7	3.6	51	1.8	†††	0.9	2	40	1.5	††	0.5	1.2	Negative	Partial remission	**Membranous Nephropathy PLA2 R negative(secondary)**