A South African Case Study Of Familial Membranoproliferative Glomerulonephritis

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Candidate's Declaration

I, Claudia Lewis Do Vale declare that this research report is my own work. It is being submitted for the degree of Masters in Medicine in the University of the Witwatersrand, Johannesburg. It has not been submitted before for any degree or examination at this or any other University.

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The 30th day of January 2015

Abstract

Membranoproliferative glomerulonephritis (MPGN) is an immune-mediated disease that is characterised by mesangial hypercellularity and endocapilliary proliferation with capillary wall remodeling which results in thickening of the glomerular basement membrane. (1) MPGN was traditionally classified on electron microscopy findings into MPGN type I, II, and III. Multiple genetic risk factors have been identified for MPGN II now referred to as dense deposit disease; however, relatively little is known regarding genetic risk factors for MPGN type I and III.

A reclassification scheme that better reflects the pathophysiology of MPGN has been implemented. This scheme divides MPGN into immune-complex-mediated and complement-mediated MPGN. Previous descriptions of familial MPGN suggest that this entity falls within the category of complement-mediated MPGN.

We describe a South African family with four family members affected with immune-complex-mediated MPGN. All other asymptomatic contactable family members were tested for proteinuria and haematuria and a pedigree for the family was established with an autosomal recessive with incomplete penetrance inheritance pattern or a multigenic inheritance pattern.

A systematic review was then performed using the search terms of "inherited MPGN" and "Familial MPGN". In the systematic review of familial MPGN from 1981-2014, nine reports containing twelve families were reviewed totaling thirteen families including the South African family. Six families were found to have immune-complex-mediated MPGN

and five families had complement-mediated MPGN. The data of two families was limited and thus couldn't be reclassified.

Most of the family members presented with nephrotic syndrome; and more family members in the complement-mediated MPGN group (41%) had a decreased serum complement versus 14% in the immune-complex-mediated group. The mean age of diagnosis, of the family members in the immune-complex-mediated group was 15 years of age with a mean age at end stage renal disease of 20 years of age. The mean age of diagnosis in the complement-mediated group was also 15 years of age with a mean age at end stage renal disease of 25 years of age. Inheritance patterns varied greatly between the studies with no clear inheritance pattern being established.

In a previous family studied, a link was found between chromosome 1q, a locus containing genes for factors affecting the complement cascade. (4) However the systematic review shows that this family falls under the reclassification of complement-mediated MPGN. Thus it is unknown if chromosome 1q is also involved in the pathogenesis of inherited immune-complex-mediated MPGN.

By describing this South African family with familial MPGN and the systematic review of familial MPGN case studies, we demonstrate that familial MPGN occurs through immune-complex-mediated and complement-mediated pathways. Based on our findings, the current classification of MPGN should be modified to include familial immune-complex-mediated MPGN as a fourth category under immune-complex-mediated MPGN. Further studies are required to assess the inheritance patterns as well as the underlying genetic abnormality related to immune-complex-mediated MPGN.

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Lastly my gratitude is given to all the family members that consented to be involved in this study.

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ABBREVIATIONS

CMJAH: Charlotte Maxeke Johannesburg Academic Hospital

MPGN: Membranoproliferative glomerulonephritis

DDD: Dense deposit disease

IM: Immune complex mediated

CM: Complement mediated

EM: Electron microscopy

LM: Light microscopy

IFM: Immunofluorescence microscopy

MAC: Membrane attack complex

ESRD: End stage renal disease

INTRODUCTION

Membranoproliferative glomerulonephritis (MPGN) is an immune mediated glomerulonephritis that is characterised histopathologically by mesangial hypercellularity, endocapilliary proliferation with capillary wall remodelling which results in thickening of the glomerular basement membrane. (1) It is often a chronic, progressive renal disease with a variable clinical presentation, usually that of an acute nephrotic or nephritic syndrome. (2) While MPGN was traditionally classified on electro-microscopy findings into MPGN type I, MPGN type II and MPGN type III, (1) the term MPGN type II was discarded for the inclusive name of dense deposit disease (DDD). (3) Multiple genetic risk factors have been identified for DDD (3), while relatively little is known about the underlying genetic risk factors for MPGN type I and type III, hence this study will focus on familial MPGN type I and III.

There is a familial incidence of 2.6- 4% of MPGN type I and type III (5) with multiple patterns of inheritance being considered, the commonest being that of an autosomal dominant or x-linked pattern of inheritance. (6,7) A familial form of MPGN type III has been identified with an autosomal dominant pattern of inheritance and it is genetically linked to band 1q31-32. (4) It has also been suggested that the gene and its function, predisposing to MPGN, may be modified by other genes that control the immune response, and hence the difference in the modes of disease expression. (7)

With recent advances in the understanding of the pathophysiology underlying the formation of MPGN, a reclassification scheme has been recommended to divide MPGN

into immune-complex-mediated MPGN and complement mediated MPGN. With this change in definition the previous descriptions of familial MPGN should also change, however due to the limited number of reported cases of familial MPGN, little is known about the epidemiology as well as the progression of disease. By describing the clinical and pathological features of a South African family with familial MPGN type I, as well as reviewing reported cases of familial MPGN between 1981 and 2014, an attempt was made at classifying familial MPGN within the new definitions, as well as reviewing the epidemiology and disease progression and lastly, further evidence is provided for the genetic basis underlying this genetic disease.

LITERATURE REVIEW

Idiopathic membranoproliferative glomerulonephritis (MPGN) is an immune mediated glomerulonephritis that is chronic and often progressive. It is characterised histopathologically by mesangial cell hypercellularity and endocapilliary proliferation with capillary wall remodelling which results in thickening of the glomerular basement membrane. MPGN commonly presents in childhood and the clinical presentation and disease course is variable, mainly due to differences in the pathogenesis of the disease. (1)

Traditionally MPGN was classified on electron-microscopy findings into three types MPGN type I; MPGN type II; MPGN type III. (1) MPGN type II (DDD) was identified as separate distinct disease entity and MPGN type III was considered a variant of MPGN type I. (6) Due to recent advances in the understanding of the pathophysiology underlying the pathogenesis of MPGN, a reclassification scheme has been recommended to divide MPGN into immune-complex-mediated MPGN and complement-mediated MPGN based on the underlying pathophysiology. (1)

The pathophysiology of both immune-complex mediated MPGN and complement mediated MPGN revolves around the complement system. The complement cascade can be initiated via three pathways, namely the alternative, classical and lectin pathways. (1) All three pathways meet at the nodal point of the pathway, namely C3, to create the enzyme complex C3 convertase.

This complex then splits C3 into C3a and C3b. C3b under factor B and D combines with C3 convertase forming more C3 convertase resulting in an amplification loop. The association of C3 convertase with C3b also generates C5 convertase which cleaves C5 into C5a and C5b, which activates the terminal complement complex pathway which forms, via

C5b-C9, the membrane-attack complex (MAC) on cell surfaces finally resulting in cell lysis of the mesangium and capillary walls, known as the injury phase. (1)

The injury phase is accompanied by an inflammatory or proliferative phase with an influx of inflammatory cells and the release of proteases and cytokines resulting in proteinuria and haematuria. Ultimately loss of fenestration occurs in the endothelial cells and the glomerular basement membrane becomes disrupted with effacement of the foot processes on podocytes.

During the reparative phase, mesangial expansion occurs due to the formation of new mesangial matrix along with the formation of a new basement membrane, which results in immune complexes, complement factors, cellular elements, and matrix material being trapped within the two basement membranes, resulting in the double contours seen along the capillary walls.

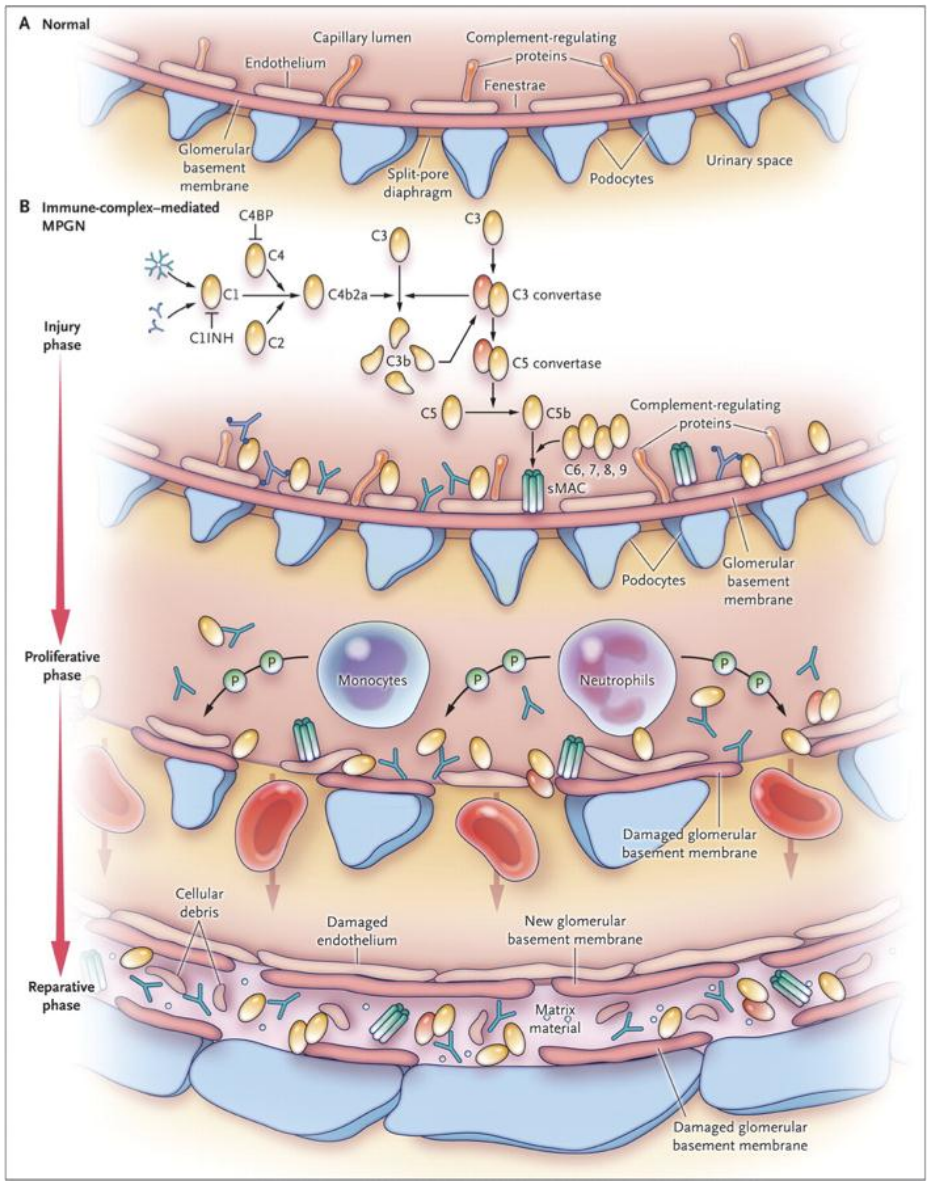

Figure 1: Normal Glomerular Capillary Wall and Immune-Complex MPGN.

Panel A is a schematic diagram of the normal glomerular capillary wall and glomerular basement membrane.

Panel B is a schematic diagram of Immune-Complex MPGN caused via activation of the classical pathway. The injury phase results from the deposition of immune complexes and complement factors of the classical and terminal pathways, followed by an influx of leukocytes, leading to a proliferative phase, with the release of cytokines and proteases (labeled P) resulting in damage to the capillary walls. Loss of fenestration occurs in the endothelial cells along with disruption of the glomerular basement membrane with the effacement of the podocyte foot processers. With repair a new basement membrane is formed, trapping immune complexes, complement factors, cellular elements, and matrix material within the two basement membranes, resulting in double contours seen along the capillary walls

Yellow oval structures indicate complement factors. The term sMAC denotes soluble membrane-attack complex.

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Thus the pathological feature found on light microscopy (LM) is the appearance of tram tracks or double contours of the basement membrane, while typically electron microscopy (EM) reveals mesangial and subendothelial deposits and occasionally intramembranous and subepithelial deposits. EM shows the replacement of the glomerular basement membrane by wavy dense osmiophilic, sausage-shaped deposits in MPGN type II (DDD). This is the only time that EM can distinguish that the MPGN is complement mediated, otherwise immunofluorescence findings are used to distinguish between complement-mediated MPGN and immune-complex-mediated MPGN. Figure 2 contains images of LM, IFM and EM features of MPGN.

The injury phase of immune complex mediated MPGN (figure 1) occurs due to the deposition of immune complexes into the glomeruli, which activates the classical pathway of the complement system, resulting in the formation of the membrane attack complex on the mesangium and capillary walls. (1) The proliferative and reparative phases then follow. Thus kidney biopsy specimens show immunoglobulin and complement deposition on IFM.

The immune complex deposition in the glomeruli are due to a.) Antigen antibody complexes from chronic infections mainly hepatitis C; b.) Increased immune complexes secondary to autoimmune disease and c.) Glomerular deposition of monoclonal immunoglobulins secondary to monoclonal gammopathies.(1)

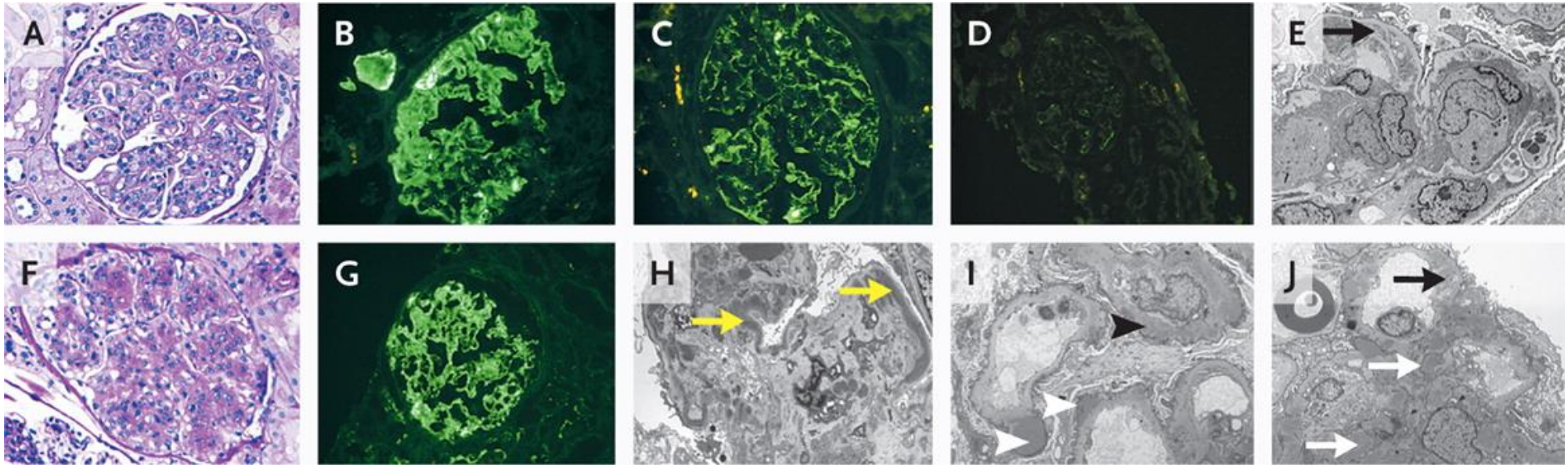

Figure 2: MPGN findings on light, immunofluorescence and electron microscopy.

A-E Shows Immune-mediated MPGN

A: Light microscopy shows an MPGN pattern of injury
B: Immunofluorescence microscopy shows positive staining for IgM
C: Immunofluorescence microscopy shows positive staining for kappa light chains.
D: Immunofluorescence microscopy shows negative staining for lambda light chains.
E: Double-contour formation and subendothelial deposits (arrow) seen on EM.

F- J shows Complement-mediated MPGN

F: MPGN pattern of injury on LM
G: Bright C3 staining on immunofluorescence microscopy with negative staining for Immunoglobulin, C1q, kappa, and lambda light chains.
H: Electron microscopy shows dense osmiophilic deposits (arrow) along the glomerular basement membranes in dense-deposit disease.
I and J: mesangial (white arrows), subendothelial (black arrows), intramembranous (black arrowhead), and subepithelial deposits (white arrowheads) and double contours in C3 glomerulonephritis on EM.

Immune-complex-mediated MPGN associated with a monoclonal gammopathy has a "monotypic immunoglobulin, usually kappa or lambda light chains restriction," (1) while MPGN associated with hepatitis C infection demonstrates IgM, IgG, C3 and kappa and lambda light chains. (1) Autoimmune diseases associated with immune-complex-mediated MPGN often have many immunoglobulins and complement proteins IgG, IgM, IgA, C1q, C3 and kappa and lambda light chains.

The injury phase of complement- mediated MPGN (figure 3) occurs due to dysregulation of the alternative complement pathway caused by autoantibodies to complement regulating proteins or mutations in those proteins. (1,3,8) In the circulation, the alternative complement cascade pathway is constantly active at low levels, thus activation is tightly protected to prevent self-harm. Different complement regulating and complement-inhibiting proteins work at different sites along the complement cascade pathway. These proteins include factors H and I, factor H related proteins 1-5, membrane cofactor protein (CD46), decay-accelerating factor (CD55), CD59, complement receptor 1 and complement receptor of the immunoglobulin superfamily. (1)

Mutations in anyone of the above can result in the dysregulation of the alternative pathway. Hence immunoglobulins are not directly involved and on immunofluorescence there is absence of immunoglobulins but shows marked complement deposition. Patients typically have hypocomplementaemia, due to the hyperactivity of the alternative complement cascade although some are recorded with normal levels.(3)

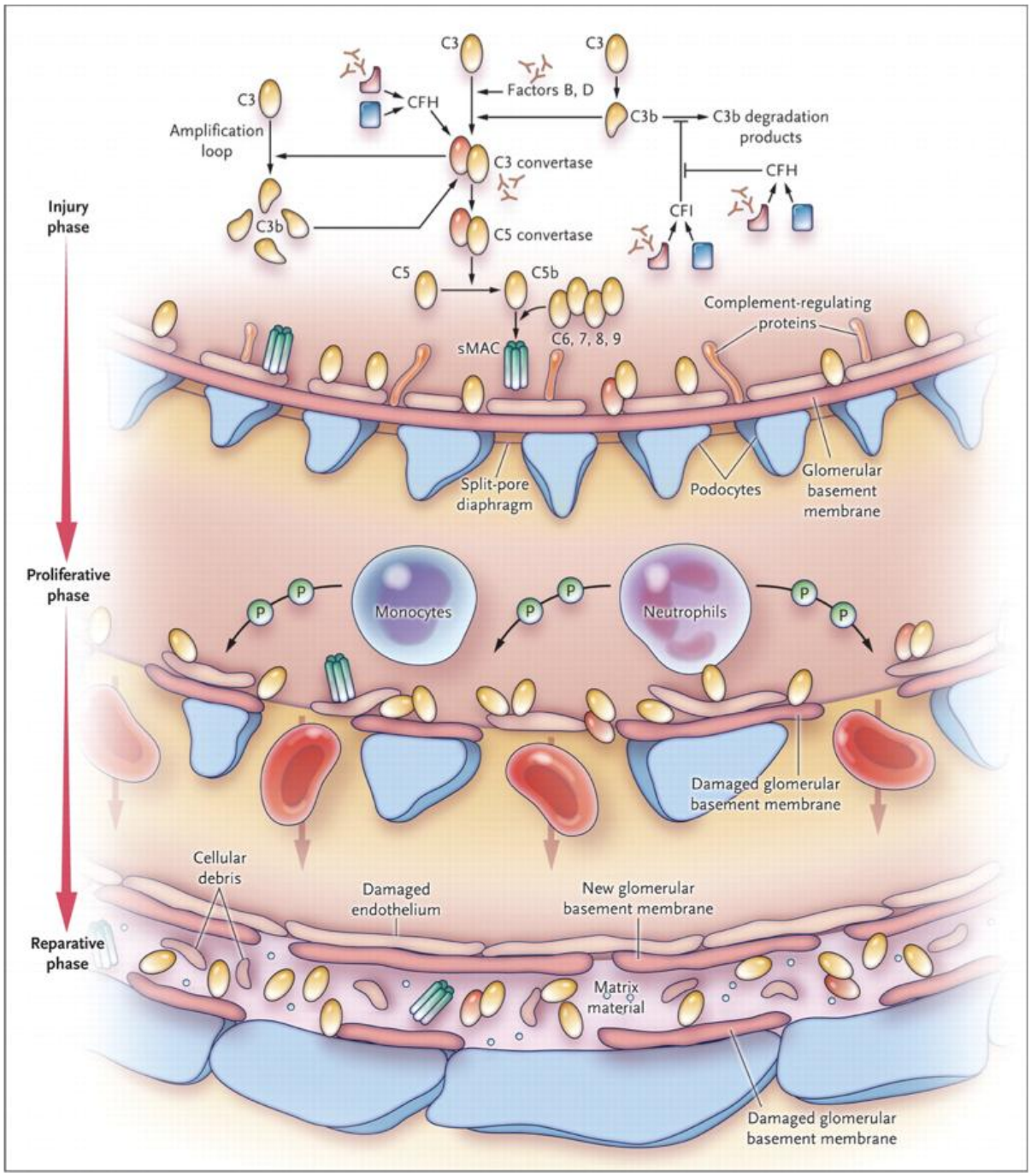

Figure 3. Complement-Mediated MPGN.

Above is a schematic diagram of MPGN associated with dysregulation of the alternative pathway.

Mutations and antibodies to complement-regulating proteins result in the deposition of complement factors of the alternative pathway and terminal complement complex causing the Injury phase. The proliferative and reparative phases are as described for immune-complex–mediated MPGN in Figure 1.

Antibodies (Y-shaped pink structures) are shown against complement factor H (CFH), factor I (CFI), factor B, and C3 convertase (C3 nephritic factor).

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From this new definition, familial MPGN Type II or DDD is now classified under complement mediated MPGN due to abnormalities caused in the function and regulation of the alternative complement pathway. (1) Complement mediated MPGN is then classified into C3 glomerulonephritis and DDD but due to the transition noted between C3 glomerulonephritis and DDD on electron microscopy, they probably represent a morphologic spectrum due to the underlying alternative complement pathway dysregulation. (9) The diagnosis should be focused on the assessment of the alternative pathway and mutations or antibodies to the complement binding proteins. (9)

MPGN type I and type III are now classified as immune complex mediated as they include both immunoglobulin deposition and complement deposition. (9) It is then further divided into the MPGN associated with chronic infections, autoimmune disease and monoclonal gammopathy. Hepatitis C and infrequently hepatitis B are the chronic viral infections attributed to the antigen antibody complexes deposited in immune complex mediated MPGN, while chronic bacterial infections such as endocarditis, infected ventriculo-atrial shunts, visceral abscesses, leprosy and meningococcal meningitis are also attributed. (9) Other suggested infections that cause immune complex mediated MPGN are malaria, schistosomiasis, mycoplasma and leishmaniasis. (9) The commonest autoimmune diseases that result in increased immune complexes are systemic lupus erythematosus, Sjogren's syndrome and rheumatoid arthritis. (9) Lastly, immune complex mediated MPGN is secondary to monoclonal gammopathies including the monoclonal gammopathy associated MPGN. (9) There is a small allowance made that if none of the aforementioned conditions exist, then it is labeled idiopathic MPGN. (9)

This classification thus excludes what was previously described as familial MPGN type I and type III. To further complicate matters, C3 glomerulonephritis with subepithelial deposits may be labeled MPGN type I, while C3 glomerulonephritis with intramembranous and subepithelial deposits may be labeled MPGN type III, (9) yet with the new classification they are identified as complement mediated MPGN, distinct from Type I and III now classified as immune mediated MPGN. (9)

Epidemiologically, MPGN is a rare cause of glomerulonephritis and accounts for 7% of adults (10) and 4-7% of children (2) with a primary renal cause of nephrotic syndrome and accounts for 7-10% of biopsy proven glomerulonephritis. (1) The familial incidence has been described as 2.6- 4% in primary MPGN type I and type III. (5) A familial form of MPGN type III has been identified with an autosomal dominant pattern of inheritance that is genetically linked to band 1q31-32. (4) The mode of inheritance has not been adequately established, with current suggestions being autosomal dominant, x-linked pattern of inheritance and autosomal recessive. (6,7) Although familial forms of MPGN type I, type II and type III disease have been reported previously, none of these reported families have been South African.

From 1976-2014 familial MPGN type I and III was reported in 30 patients. This diagnosis was established after excluding other causes of MPGN and the type of MPGN was confirmed on light microscopy (LM) and the type was based electron microscopy (EM) findings. In the first study Berry et al. (11) presented two unrelated sibships. All four patients presented within the first decade of life with proteinuria and hypertension.

In the first family “The M siblings” the brother (JM) was found to have MPGN type III on LM and EM and on immunoflourscence there was moderate deposition of C3 and a small amount of IgG. His sister (PM) had MPGN type I on LM and EM and on immunoflourscence there was marked deposition of C3 and a small amount of IgG. The serum C3 levels were low for both siblings at diagnosis, however PM’s serum C3 had normalised at the time of publication. Both siblings were treated and maintained on alternate day prednisone. They had improved clinically by the time of the article’s publication.(11)

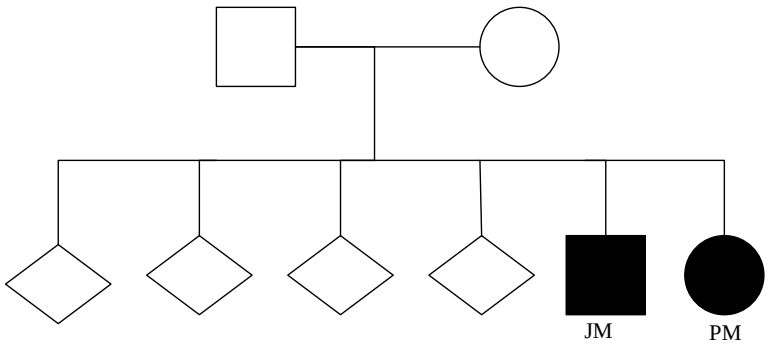
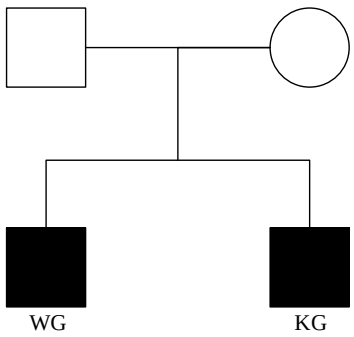


Figure 4: Pedigree M family Berry et al.



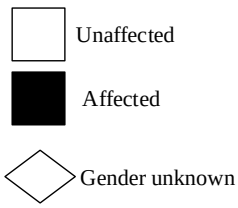


Figure 5: Pedigree G family Berry et al.

The second sibship were labeled as “The G siblings”. They were two brothers who were discovered incidentally when WG was found to be anaemic, hypertensive and proteinuric

on a routine preschool physical examination. His bother KG had previously been anaemic, was then worked up for renal disease and was found to have severe renal dysfunction. Neither brother had haematuria. Both were found to have MPGN type I on LM and EM, and on IFM they were both found to have marked IgM and IgG deposition.

KG had marked C3 deposition while WG had minimal C3 deposition. However the biopsy available from KG was the biopsy done 4 years after presentation and not the initial biopsy. Throughout their diagnosis and followup, both brothers' serum C3 levels remained normal. Both brothers were placed on therapy with alternate day prednisone. However their hypertension worsened on therapy and they both had a slow decline in renal function.(11)

The conclusions drawn by Berry et al. (11) was that there was likely an underlying genetic basis for the disease but that exposure to certain enviromental factors would result in disease expression. Due to the different types of MPGN in the sibship of the M family, they postulated that MPGN is multigenic in origin, modified by other genes which regulate the immune responses resulting in the different types of disease expression. (11) Interestingly in the G family, KG and his faher had C2 deficiency. However KG has an affected brother who was not C2 deficient and his father, who was C2 deficient, had no disease. This indicated that in this family the C2 deficiency was not associated with a predisposition to MPGN (11) as previously shown by Kim et al.(12)

Stutchfield et al. (13) reported two related male patients with type 1 MPGN and they surmised that the inheritance was an x-linked recessive disorder. Both patients were proteinuric and presented within the first two years of life. The first patient (LA) presented

with persistent proteinuria originally detected on routine urine testing. He was found to be normotensive and had no haematuria. He had normal renal function as well as normal serum C3 levels. He later developed hypertension and had slowly deteriorating renal function. His serum C3 level however remained consistently normal. On renal biopsy the LM and EM findings were consistent with MPGN type 1. On immunofluorescence he had depositis of IgG, IgM and minimal C3.(13)

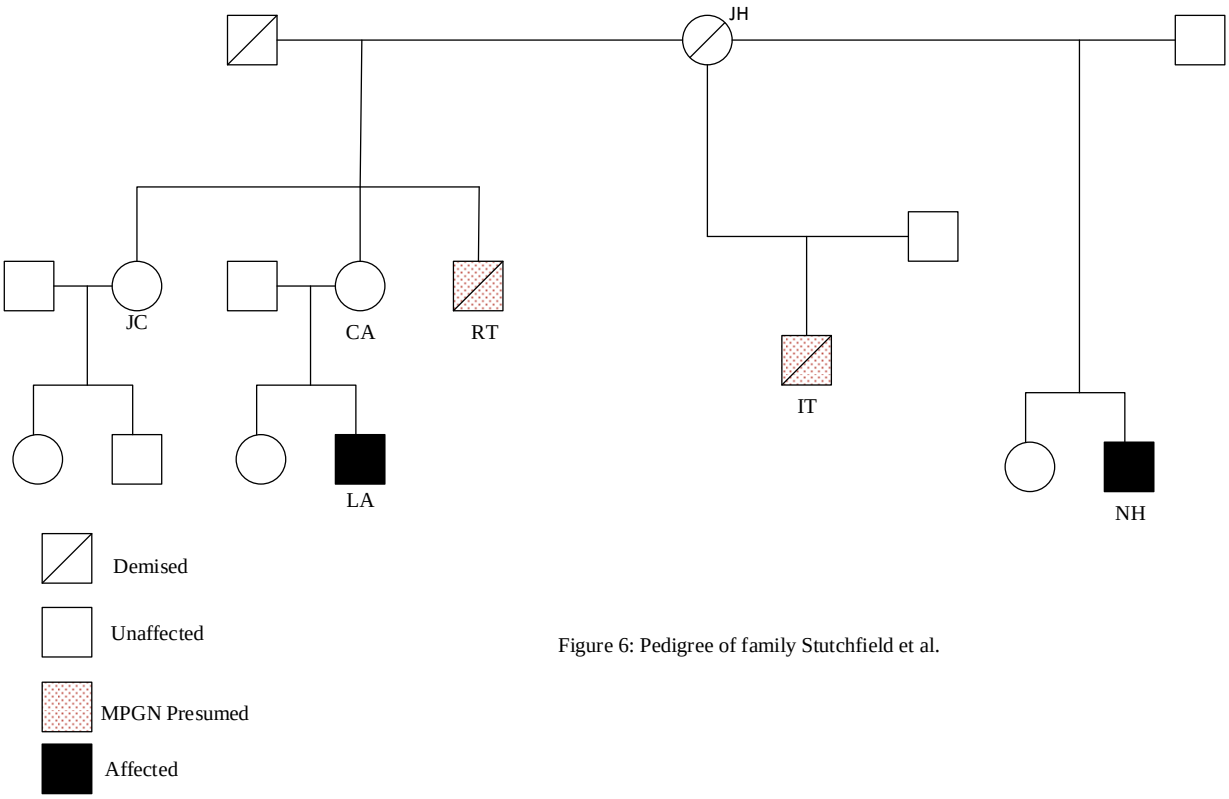


Figure 6: Pedigree of family Stutchfield et al.

The second patient (NH), the maternal uncle of the first patient (LA), presented with bipedal oedema and persistant proteinuria. He was normotensive, had microscopic haematuria and normal renal function. He was also found to have normal serum C3 levels. The renal biopsy features were that of MPGN type 1 on LM and EM. Immunofluorescence however was not done. He received cyclophosphamide but the proteinuria persisted and his renal function gradually deteriorated. He later became hypertensive. Throughout his course

his serum C3 and C4 levels remained normal. He demised from hypertensive encephalopathy.(13)

In terms of the family's pedigree, the grandmother (JH) of LA, the mother of NH, had only one son (NH) who had biopsy proven MPGN. However her two other sons from different fathers demised at a young age following nephritic illnesses. Her daughter (CA), a half sister to NH, and the mother to LA, was healthy. Four of the grandmother's (JH) ten brothers died at a young age, with two having symptoms suggestive of nephritic/nephrotic illness. Furthermore, one of the grandmother's (JH) sisters had a son who also died in the first decade of life from a similar illness. This was the first study with patients diagnosed with MPGN under the age of two, reflecting an underlying genetic basis for the disease. Together with the family pedigree an assesment was made of the mode of inheritance being x-linked recessive.(13)

Sherwood et al. (14) described a father and son with MPGN, that the authors describe as an autosomal dominant pattern of inheritance. The son at the age of four, was found to have proteinuria on admission for a tonsillectomy. He was normotensive, had haematuria and normal serum C3 and C4 levels. Renal ultrasound was normal and he also had normal renal function at diagnosis. A renal biopsy was done when the son was 5 years old. While on LM and EM the features were consistent with MPGN type I, immunofluorescence was however negative for IgG, IgA, IgM and C3. His condition remained stable and he was not receiving any treatment.(14)

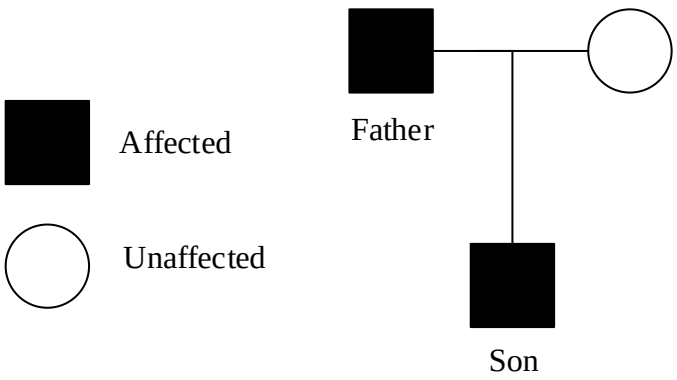


Figure 7: Pedigree of family Sherwood et al.

His father at the age of twenty two years was found to be proteinuric and hypertensive. He had a renal biopsy eight years later when he had end stage renal failure, which on LM and EM had features of end stage renal disease due to MPGN. The type of MPGN was not mentioned. Three years later at the age of thirty three, the father underwent renal transplantation. No information is supplied regarding serum C3 and C4 levels, nor regarding his treatment. Both father and son were found to have unusual facies as well as unusual telangiectasia not associated with any known syndrome. The final conclusion from the authors was that the mode of inheritance for this family was autosomal dominant. They distinguished their family from the previous study by Stutchfiel et al. due to the unusual skin condition seen in father and son.(14)

Bakkalogu et al. (7) described six patients from two families with MPGN. Family one (G family) had first-degree consanguinity in the parents. All four sons were affected.The two daughters and parents were unaffected. All four of the affected sons presented within the first decade of life with proteinuria. Two (SG and AG) had hypertension at diagnosis and one son (BG) developed hypertension during the course of the disease. The youngest son

(IG) presented at the age of 10 months. Two of the brothers (SG and BG) presented at the age of three years and the other brother (AG) was seven years old at diagnosis. All had normal renal function at diagnosis, however the patient AG had progressive worsening renal function at the time of publication. All four brothers had normal serum C3 and C4.

Only three of the brothers' biopsy results were available as the eldest brother (AG) had had the diagnosis of MPGN made previously. Of the three biopsies, all were in keeping with MPGN type I. In the patient SG, no immunoflourescence was done. In the other two brothers (BG and IG), there was mainly C3 deposition. One of the father's (DG) brothers died of an illness suggestive of nephritic syndrome; no further information was available about this family member. (7)

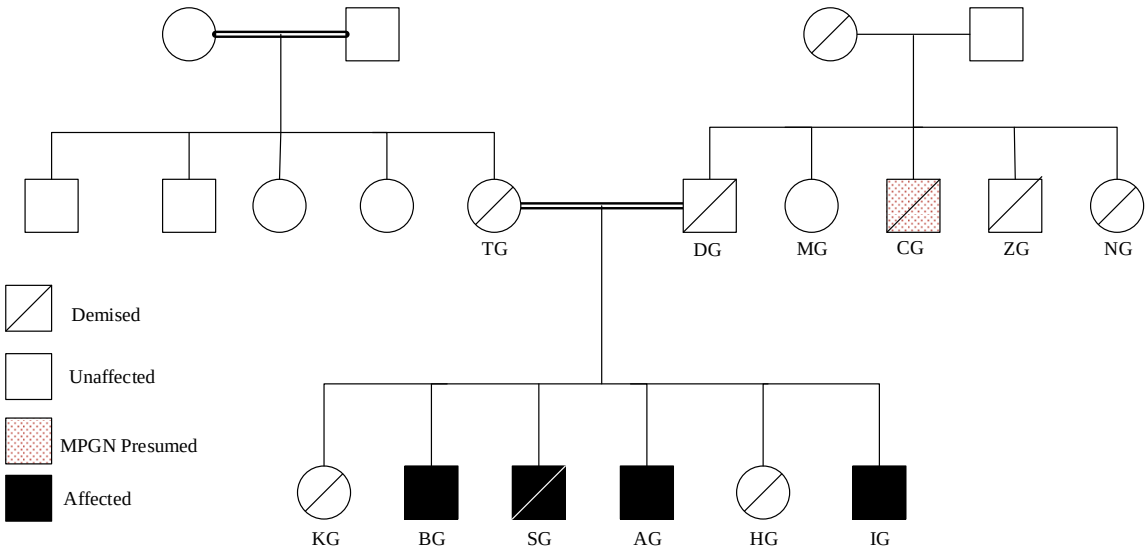


Figure 8: Pedigree of the G family Bakkalogu et al.

The second family “The Y family” had unrelated parents and four sons and one daughter. Two brothers presented with hypertension, proteinuria and haematuria at the age of nine (MY) and thirteen (FY). Their initial serum C3 and C4 levels were low but subsequently normalised. On biopsy, the LM and EM finding were consistent with MPGN type I and on immunoflourescence, MY had only C3 deposition while FY had C3 and IgA deposition. No abnormalities were detected in the serum complement profile in both families. On review of both families, the mode of inheritence is proposed to be autosomal dominant or an X-linked inheritance with incomplete penetrance, as members in more than one generation were affected. However there was a different progression of disease between MY and FY which the authors postulated as indicating a multigenic orgin for MPGN, with a gene predisposing to MPGN but requiring modification by other genes affecting immune control, resulting in the different modes of disease expression (7) , a similar finding to that of Berry et al.(11)

Abderrahim et al. (15) reported two brothers who were both diagnosed with MPGN I. There was first degree consanguinity in the parents. The first patient HL presented at the age of 17 with hypertension, bilateral pitting oedema, proteinuria and macroscopic haematuria. He had a normal renal ultrasound and normal serum C3 and C4 and mild renal dysfunction. His renal biopsy on LM and EM was consistent with MPGN type I. There was no comment made regarding immunoflourescence. HL was started on antiplatelet agents and beta blockers. Eighteen months later his renal function had normalised and he had trace proteinuria. His complement levels were normal.(15)

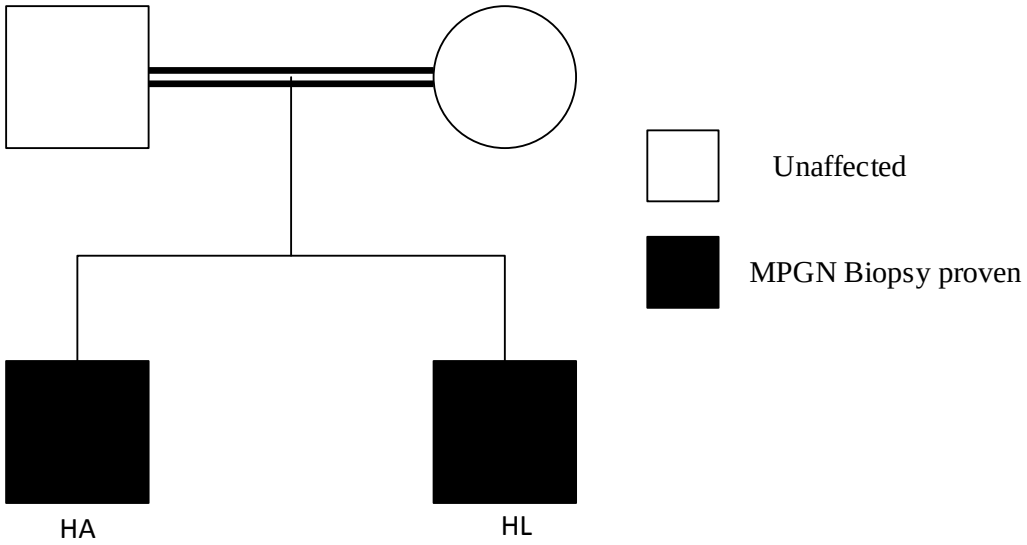


Figure 9: Pedigree of family Abderrahim et al.

HL's elder brother HA presented with hypertension, haematuria and proteinuria at the age of eighteen. His renal biopsy findinging on LM and EM were in keeping with MPGN type I. He had renal failure at diagnosis and demised three years later from end stage renal disease. Limited data is available regarding HA as he was diagnosed and treated at a different hospital than that of the authors. Regarding the presentation and progress of the two brothers, the authors postulated that familial MPGN is a multifactorial disease. (15)

Bogdanovic et al. (5) reported two siblings with MPGN. Patient 1 was a boy who was 5 years old when he presented with bipedal oedema, hypertension, haematuria and proteinuria. He had low serum C3 and C4 levels. LM and EM findings were of MPGN type I. Immunoflourescence showed IgG, IgM, IgA and C3 deposits. Initally he was started on alternate day prednisone, followed by cyclosporine and then cyclophosphamide. His nephrotic syndrome resolved when he was nine, but he remained with residual proteinuria.

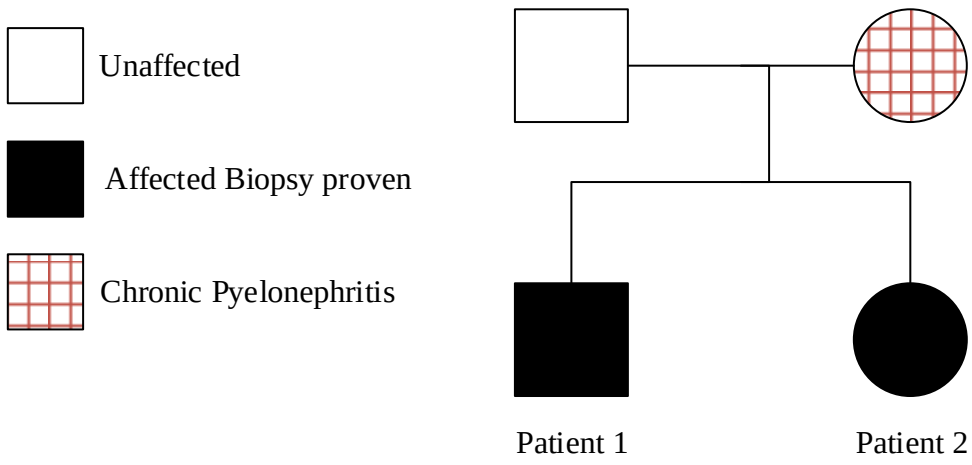


Figure 10: Pedigree of family Bogdanovic et al.

Patient 2 was a girl who presented only with proteinuria when she was at the age of 3 years. Her disease progressed and when she was six years old, she presented with nephrotic syndrome. Her serum C3 and C4 levels were persistently normal. On LM and EM, she had findings in keeping with MPGN type III. She had C3, IgG, IgM and IgA deposits on immunoflourescence. She received the same treatment as her brother, but she remained nephrotic and her renal function declined at the age of seven and a half years.

In terms of the family history, the parents were unrelated and the father was healthy. The mother developed hypertension and advanced renal failure at the age of eighteen during her first pregnancy, which was terminated by miscarriage. Her renal function declined and three years later regular haemodialysis was started. Her renal failure after workup was attributed to chronic pyelonephritis. She was transplanted at the age of tewnty-two and her graft renal function was excellent. She went on to deliver her two children post transplantation. Autosomal dominant disease possibly associated with MPGN was excluded in this family. (5)

The authors reviewed the other families previously published with MPGN and found no reported abnormalities of complement which corresponded with their patients. They also found that different HLA haplotypes were associated with MPGN in the different studies. The highest frequency was that of HLA-A2. However, previously it was noted that patients with haplotype HLA-B8 had a poorer prognosis for kidney function. However, their patients had HLA-A24, B27, Bw4, DR11, DR52 and DQ3 in common, and while having similar clinical pictures, they had different types of MPGN and despite the same treatment, they had markedly different outcomes. Thus, their finding was that the mode of inheritance is probably multigenic in orgin, with an underlying gene predisposing to MPGN but modified by other genes. (5)

Motoyama et al. (6) published a case report of MPGN type I diagnosed in a mother and her daughter. Case 1, the daughter at the age of fourteen, had microscopic haematuria and proteinuria detected on routine school urinary testing. She was normotensive and had low serum C3 levels, but normal C4 levels. LM findings on biopsy were that of MPGN type I. No glomeruli were included in the specimen for EM. On immunoflourescence there were only C3 deposits. She was treated with methylprednisone for three days followed by prednisone. The proteinuria disappeared and the prednisone was stopped in a month. She continued to have microscopic haematuria and hypocomplementaemia. (6)

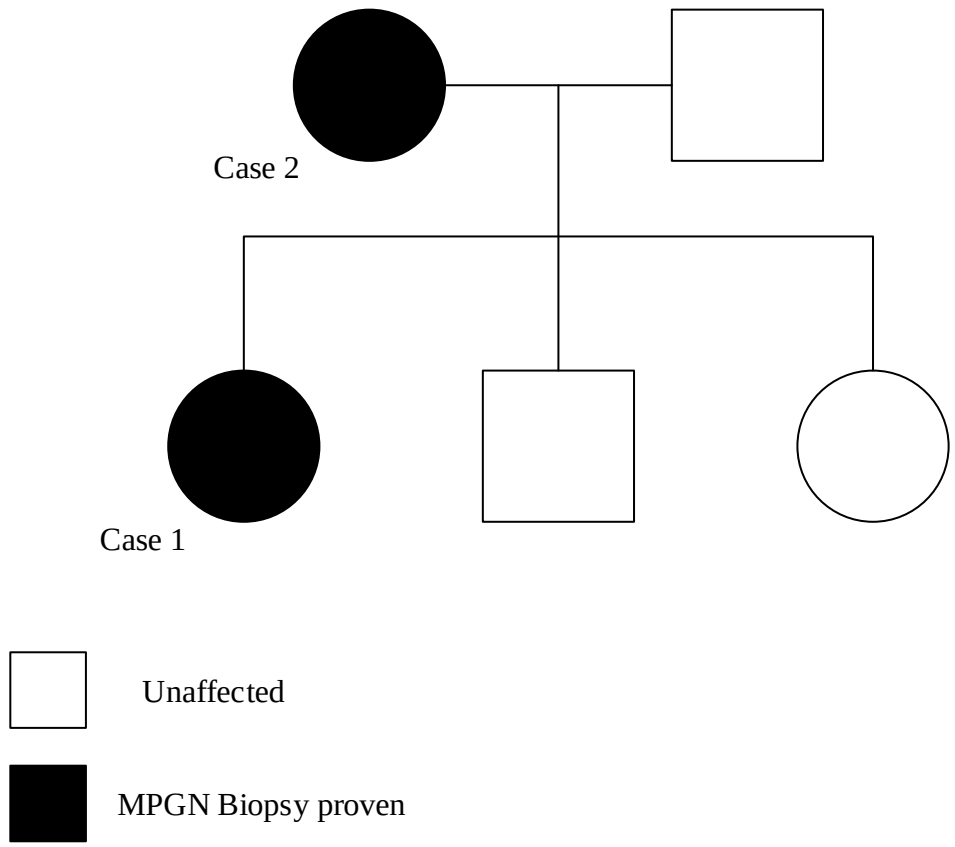


Figure 11: Pedigree of family Motoyama et al.

Case 2, the mother, developed oedema, hypertension, proteinuria, and microscopic haematuria when she was nine years old. Both serum C3 and C4 levels were low. The oedema and hypertension improved a month later but the haematuria, proteinuria and hypocomplementaemia persisted. The renal biopsy findings on LM and EM were in keeping with MPGN type I and on immunoflourescence, only C3 deposits were found. She was started on steroid therapy but continued to have proteinuria. She defaulted therapy at the age of fifteen and presented again at the age of twenty four, when she was found to be normotensive, with no oedema but persistent proteinuria. She had low serum C3 and normal serum C4 but mild renal dysfunction.

She was started on dipyridamole and had three successful pregnancies, but developed nephrotic syndrome in the first and third pregnancies. During the last pregnancy her renal function declined and she received methylprednisone and her renal function improved. At the time of publication she had normal renal function with low serum C3 and mild proteinuria. Only one of her daughters had MPGN type I, the other children were healthy. The authors postulated that the mode of inheritance is unclear, and while there may be an underlying genetic basis, it is likely that enviromental factors are a cause, due to the discrepencies in clinical and pathological findings in family members. (6)

The last two familial studies are both from Ireland. The first family described by Neary et al. the index case (subject 105), a 51 year old male, presented with hypertension, haematuria, proteinuria and renal dysfunction. Twelve years earlier he had been healthy with no haematuria or proteinuria on donation of a kidney to his son (subject 213). While his complement profile was normal, his renal biopsy on LM had features consistent with MPGN and EM features suggested it to be of type III. On IFM there was only C3 deposition. He was treated with steroids and pulsed with cyclophosphamide and still has persistent renal dysfunction.

His son had presented at the age of four years with nephrotic syndrome unresponsive to steriods. He also had a low serum C3 and normal C4 and was found to have microscopic heamaturia. His renal biopsy on IFM showed C3 deposition and on EM the MPGN was listed as type III MPGN with subendothelial, intramembranous and subepithelial basement membrane depositis. Six years later, at the age of ten years he received a kidney transplant from his father for ESRD. On a renal biopsy specimen of the transplanted kidney, two years after transplant, the speciment showed MPGN type III with C3 deposition on IFM.

Six years post transplant he developed graft failure and receieved a second graft. It is not stated whether it was cadaveric or familial tranplant. Up to publication he was doing well but remained proteinuric.

His brother (subject 212) and sister (subject 214) were investigated for nephrotic syndrome. Both of their renal biopsy specimens were in keeping with MPGN type I. Both had normal serum complement levels and normal renal function. Their paternal aunt (subject 103) also developed ESRD at 51 years of age and her biopsy, done at the age of twenty-six years, was also consistent with MPGN. She was found to have normal serum complement and received a renal transplant at the age of fifty-four years.

The index patient's sister (subject 107) and niece (subject 223) , on screening were found to have haematuria and proteinuria and on renal biopsy MPGN type III. They both also had normal serum complement levels.

Neary et al. in a follow up study of this study found a linkage of chromosome 1q to MPGN type III with an autosomal dominant pattern of inheritance. (4) This locus was found to contain genes that code regulators of the complement pathway. The authors concluded that MPGN type III was more likely to be steroid resistant and typically progressed to ESRD within ten years after presentation. (4)

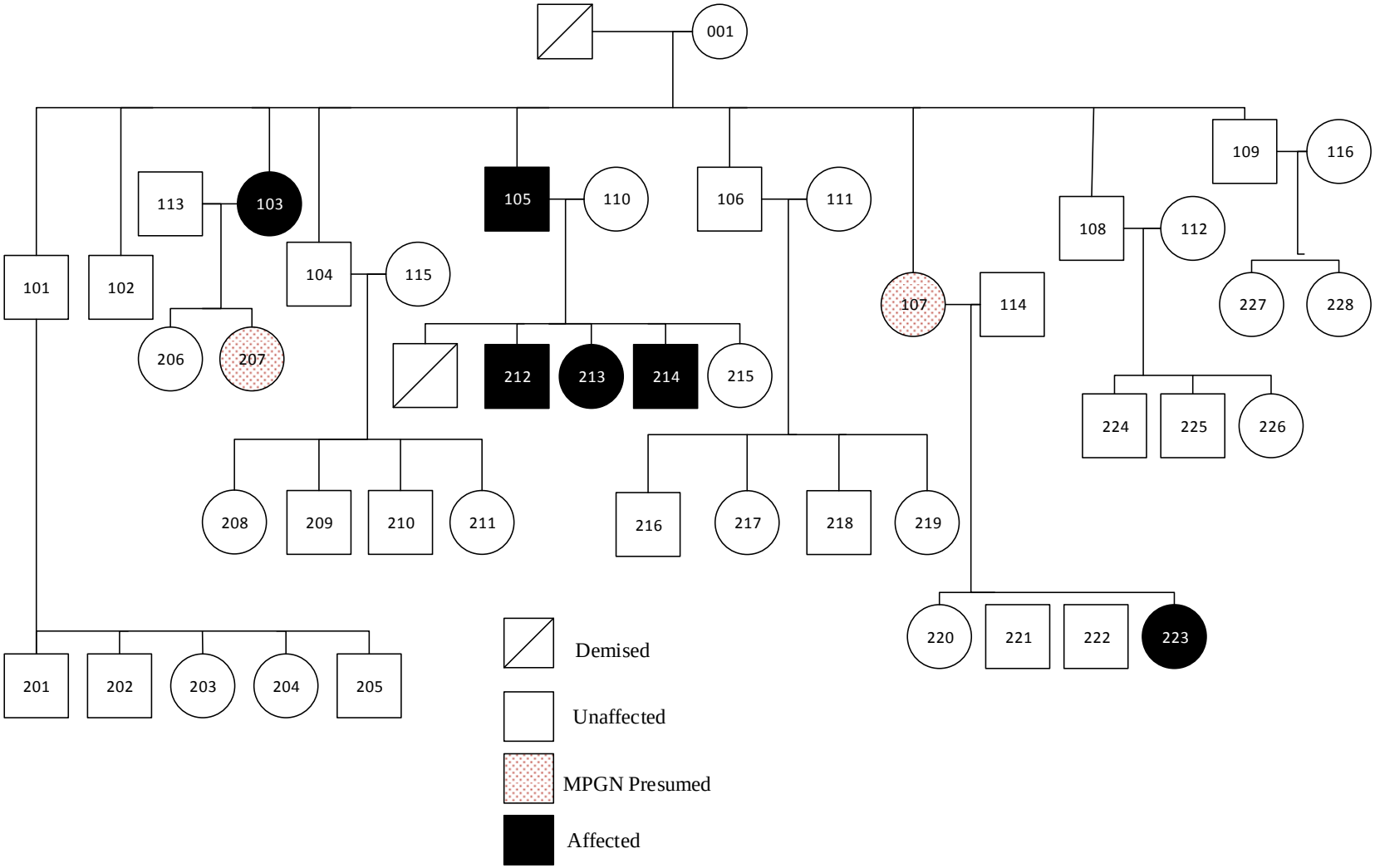


Figure 12: Pedigree of family Neary et al.

Redahan et al. described 3 separate families all with familial MPGN, however the third family was diagnosed with MPGN of dense deposit disease type (type II MPGN) and thus is excluded from this study. The first family had two affected members.

The index case was 16years of age when she presented in renal failure. She had no other medical history and on renal biopsy was found to have MPGN with immune complex deposition. Within five years she had progressed to ESRD and was initiated on RRT. She received a cadaveric transplant a year later at the age of 22 years which failed due to chronic allograft nephropathy, which also caused the failure of her second cadaveric transplant. Her third graft remained well functioning at time of the publication. No evidence of recurrence was found in any of the grafts.

Her brother was diagnosed with renal disease at the age of eighteen and his biopsy showed MPGN with immune complex deposition. He received a cadaveric transplant at the age of twenty two years after starting RRT at the age of twenty-one years.(16)

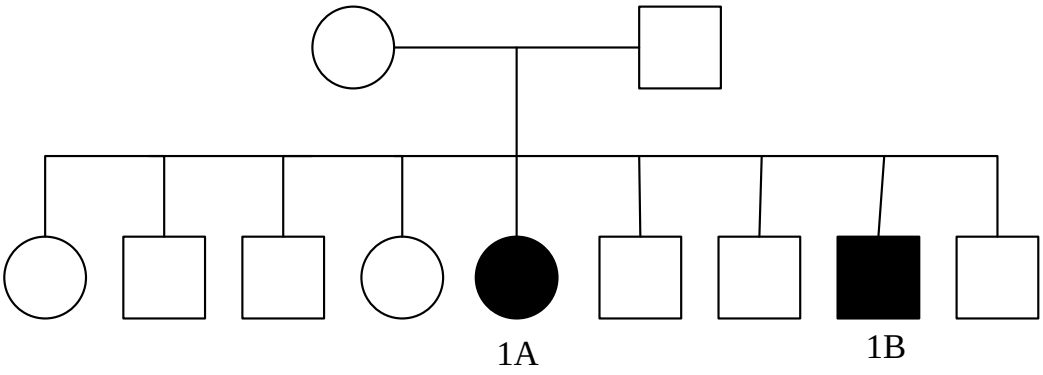


Figure 12: Pedigree of family 1 Redahan et al.

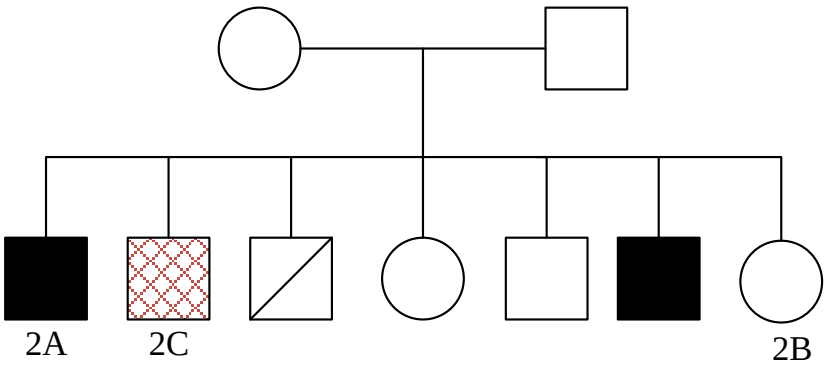
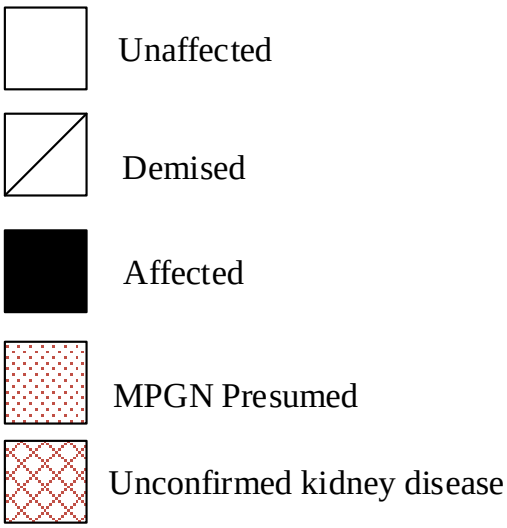


Figure 13: Pedigree of family 2 Redahan et al.



The second family's index case was a twenty-two year old male (case2A) who presented with a severe headache, hypertension and renal dysfunction. He was found to have haematuria, proteinuria and low serum complement levels. On renal biopsy he was found to have a moderate amount of immunoglobulin and complement deposition. Within twelve months he had progressed to ESRD and started RRT. A year later he received a kidney transplant from a living related donor, one of his siblings.(16)

A routine examination of the youngest brother (case 2B) revealed proteinuria and a renal biopsy was done, which demonstrated MPGN with immunoglobulin and complement deposition. At seventeen years of age he received a kidney transplant from one of his siblings, although it was done preemptively. Six years later he received a second transplant, from another sibling, after graft failure occurred due to disease recurrence. The second eldest brother (case 2C) developed microscopic haematuria at the age of thirty-one years and underwent a renal biopsy with had features of an IgA nephropathy. He however remained well and didn't progress in terms of his renal disease. Redahan et al then discusses the possible inheritance pattern of family 1 as autosomal recessive and family 2 as x-linked or autosomal recessive.(16)

From the above, it can be seen that very few families world wide have been described with familial MPGN and none have been South African. Futhermore, since the new classification of MPGN has come into place, there is increasing confusion as to which category familial MPGN falls into. By examining this South African family and doing a systematic review of the literature, a larger case series is obtained which allows for an improved understanding of the conundrum that is familial MPGN type I and Type III.

AIMS

1. The aim of this study is to determine the incidence of MPGN within the family of our index patient as well as to assess if there is a Mendelian inheritance pattern within this family.
2. Further more a systematic review was undertaken to review the available literature on familial MPGN and to classify familial MPGN within the new definitions of MPGN.

OBJECTIVES

1. Determine the incidence of MPGN within the family of our index patient.
2. Assess the Mendelian inheritance pattern within this family
3. Review and compare with previous published studies.
4. Classify familial MPGN

METHODS

Ethical Approval

Ethics approval was obtained from the Human Research Ethics Committee (Medical) of the University of the Witwatersrand, certificate number M120446, for a prospective study of the available family members of the index patient and a retrospective study of those family members already worked up or diagnosed and been treated for MPGN type1.

Study Population

All contactable family members of the index patient that consented to participate in the study were included. The four family members, including the one deceased family member, that attended the Renal Unit at the Charlotte Maxeke Johannesburg Academic Hospital (CMJAH) were also included as part of the retrospective study.

Data Collection

The study was an open study with the primary investigator knowing the results for all participants included in the study. With regards to the data collection, each participant was given a coded number and all data collected was kept under this code to maintain confidentiality, with only the primary investigator knowing the coding system.

The data collected from the Renal Unit at CMJAH for those family members already worked up for the disease, included the patient's history, clinical presentation, blood

results as well as their renal biopsy results. All other asymptomatic contactable family members that consented to participate in the study were included and participants provided a urine sample, which was tested for proteinuria and haematuria with Uricheck M10 Urine Reagent Strips Omnipharma (Pty) Ltd.

Histories were obtained from the asymptomatic family members to determine if other diseases and comorbidities were present that would affect the results. If a co-morbidity was found, they were excluded from the study. A blood sample in an EDTA tube was also taken and kept at minus 20 degrees Celsius for DNA extraction for a follow up study to assess if there is an underlying genetic mutation within this family. If family members were found to have proteinuria and/or haematuria with no other cause for the proteinuria and/or haematuria, they were considered positive for this study and referred for further work up including a renal biopsy at CMJAH Renal Unit. The data obtained from family members diagnosed with MPGN was collated with the information available from previous reports.

Systematic review

For the Systematic review, the two following terms were searched in PubMed separately, familial MPGN and inherited MPGN. The term mesangiocapilliary is used interchangeably for MPGN on PubMed, and using the term mesangiocapilliary glomerulonephritis in place of MPGN has the same results as for the MPGN search. Combining the two searches, ninety-seven articles were found but only ten were applicable. The eighty-seven articles that were excluded pertained studies regarding animal MPGN studies, Type II MPGN (DDD) or C3 nephropathy, and studies that were MPGN associated with other illnesses

including those associated with haemolytic uraemic syndrome and familial Mediterranean fever. The reports that did not include actual familial studies in the research report were also excluded. Of those ten articles that were applicable, two were concerning the same family (4,17) , one study was a descriptive study (17) and the other looked at the genetics pertaining to the family studied. (4) Reports of MPGN in siblings prior to 1980 had very limited data especially regarding the biopsy results and immunofluorescence and as such they were unable to be reclassified according to the new definitions of MPGN and thus were also excluded.

A Spanish study by Robles et al. (18) appeared to be applicable, however all attempts to obtain the study including writing to the authors has been unsuccessful. The studies that were applicable and able to be obtained were assessed and their data combined and where possible reclassified according to the immunofluorescence results. In the report by Redahan et al. (16) Family 3 was excluded from the systematic review as the family members were diagnosed with MPGN type II which was an exclusion criteria for the systematic review.

RESULTS

The Study Family

17 of the 20 contactable family members were available and consented to participate in the study. Four members (22%) were affected. The three who were proteinuric and without any comorbidities were the three members currently attending the renal unit at CMJAH. The demographics and clinical presentation of the affected family members can be found in table 1. Their family tree can be found in figure 10.

Table 1: Demographics and clinical data

Patient Designation	**304**	**405**	**404**	**413***
Gender	Male	Male	Male	Female
Age at diagnosis (years)	29	15	18	13
Follow up (years)	1	8	5	8
Hypertension	Yes	No	No	Yes
Hypertensive at follow up	Yes	Yes	No	Yes
Haematuria	Yes	Yes	Yes	Yes
Persistant Haematuria	Yes	Yes	Yes	Yes
Proteinuria	Yes	Yes	Yes	Yes
Urine protein g/24hr	4.9	14.0	10.4	3+ **
Persistant Proteinuria	Yes	Yes	Yes	Yes
ESRD age	Demised before follow up	19	No	No

Table with the patient demographics, clinical presentation, residual clinical characteristics and age at diagnosis of end stage renal disease (ESRD) IP: Index Patient
* Index patient; **only data from qualitative urinanalysis available as patient previously diagnosed at another institution.

Our index patient (413) presented to the renal unit at CMJAH at the age of seventeen with nephrotic syndrome. At the age of thirteen years, she had presented at another institution with bipedal oedema, hypertension and proteinuria and was diagnosed with nephrotic syndrome secondary to idiopathic MPGN type I and had been on oral steroids (prednisone 5mg alternate days) since then. Despite the corticosteroid use, she remained proteinuric

and was admitted by the renal unit at CMJAH for a repeat renal biopsy. The rest of her medication included perindopril 8mg daily, telmisartan 40mg daily and atorvastatin 20mg daily. She had normal renal function at both renal biopsies and her serum C3 and C4 levels have always remained normal. She had no co-morbidities her initial lab results can be found in table 2.

Table 2: Laboratory data

Patient Designation	304	405	404	413*
Serum Creatinine umol/l	238	97	71	14
Serum Albumin g/l	16	34	39	26
Serum C3	Normal	Normal	Normal	Normal
Serum C4	Normal	Normal	Normal	Normal
GFR at diagnosis mL/min	32	71	128	182
Creatinine at follow up umol/L	265	906	93	170
GFR at follow up mL/min	29	8	96	40

Table with the laboratory data pertaining to the affected family members
* Index patient;

The light microscopy and immunofluorescence features of her renal biopsy were in keeping with an immune-complex mediated glomerulonephritis with a membranoproliferative reaction pattern favoured to represent those of MPGN type I. As shown in table 3, she had IgG and C3 deposition on IF thereby reclassifying her as an immune-complex mediated MPGN. All other causes of proteinuria were excluded as well as other causes of immune-complex mediated MPGN. Despite immunosuppressive treatment (tacrolimus and glucocorticoids at higher doses) her renal function continued to steadily decline to a glomerular filtration rate (GFR) of 40mL/min (originally 182mL/min) and she remained proteinuric. She did not develop any complications post biopsy nor from her treatment.

Table 3: Renal Biopsy Features and MPGN Classification					
Patient Designation	Classification at diagnosis	Immunofluorescence Microscopy			New Classification
		IgG	IgM	C3	
304	MPGN	Not done	Not done	Not done	IM features on light microscopy
405	MPGN TYPE I	Yes	Yes	Yes	IM
404	ATN	No	No	No	ATN
413*	MPGN TYPE 1	Yes	No	Yes	IM
Table with the renal biopsy features and the original diagnosis made with the old classification and the new classification based on the biopsy results. * Index patient;					
ATN: Acute tubular necrosis; IM: Immune complex mediated					

Two of her first cousins (404 and 405) who are brothers, and her one maternal uncle (304) had also attended the renal unit at CMJAH. Her two cousins were from a consanguineous marriage, with their parents being first cousins. 405 presented prior to his brother (404) to the CMJAH paediatric unit, at the age of 4 years, with jaundice and splenomegaly following an acute hepatitis A infection. On a follow up visit at 11 years of age, he was found to have asymptomatic microscopic haematuria and he was referred to CMJAH paediatric renal unit.

He remained asymptomatic and all workup was normal, a renal biopsy was not done. He then moved to Cape Town. At the age of 15 years, he returned to the paediatric unit at CMJAH with anasarca and hypertension and was found to have marked proteinuria and haematuria and was worked up for nephrotic syndrome. He had normal serum C3 and C4 levels and a normal GFR. All other work up for his nephrotic syndrome was negative. He also tested negative for all causes of immune-complex mediated MPGN. He had a normal renal and abdominal ultrasound and the portal hypertension and splenomegaly, previously diagnosed at four years of age, had all resolved and were normal.

His renal biopsy's histological features were in keeping with an immune-complex mediated glomerulonephritis with a membranoproliferative pattern and a mild to moderate acute tubular necrosis. The electron microscopy findings were supportive of an immune complex mediated MPGN type 1. IFM showed marked IgG deposition, IgM and C3 staining thereby his new classification was thus immune-complex mediated MPGN.

He was started on daily oral prednisone at 1mg/kg and had three cycles of cyclophosphamide, which resulted in resolution of the haematuria and a decrease in the proteinuria although he still remained proteinuric. The oral prednisone was then weaned and stopped after 11 months of treatment. Seven months later he was then restarted on oral prednisone and Mycophenolate Mofetil (trade name: Cell Cept) 500 mg daily as his proteinuria had increased and he was transferred to the adult renal unit at CMJAH. Despite immunosuppressive treatment he remained proteinuric and had a progressive decline in renal function ultimately resulting in end stage renal disease (ESRD) four years after diagnosis. He is currently on renal replacement therapy and awaiting renal transplantation.

404, brother to 405, presented at the age of nineteen years with nephrotic syndrome. His renal function was normal at the time and his serum C3 was slightly raised and he had a normal serum C4. His work up for all causes of nephrotic syndrome was negative and he had a normal renal and abdominal ultrasound. On renal biopsy LM and EM features were in keeping of an acute tubular necrosis (ATN). On immunofluorescence there was no complement and immunoglobulin deposition staining. Despite extensive workup, no cause of the ATN was found and a final assessment of mild acute tubular necrosis of unknown cause was made. He however continued to have proteinuria and was started on daily prednisone at 1mg/kg. The proteinuria gradually decreased and after the fourteen month,

the prednisone was stopped. His blood pressure also normalized on treatment. After the prednisone was stopped he has followed up at the renal unit irregularly due to work commitments.

In 2013 he returned to the unit and was found have mild proteinuria and his GFR has steadily declined. At a previous visit, his GFR had been lower than his original GFR but no follow up occurred due to the patient being lost to follow up. His GFR has been steadily declining, although not at the same rate as his younger brother, and his most current GFR is 93ml/min (original GFR at presentation was 128ml/min). Due to his work commitments, he was unable to attend the renal unit regularly and there has been a delay in obtaining a repeat renal biopsy. In light of the fact that he presented with nephrotic syndrome and the biopsy results, despite being reviewed, were out of keeping with his nephrotic syndrome and as currently he remains proteinuric , he is undergoing active work up again for a repeat renal biopsy.

Six years earlier 304, the maternal uncle of our index patient, was referred to CMJAH at the age of twenty nine years after presenting to a private health care facility where he was diagnosed with nephrotic syndrome with renal failure. He was unemployed and had no funds for medical care and hence he had not sought medical care sooner. He was hypertensive and had anasarca. There were no other abnormalities noted on examination. He had normal serum C3 and C4 and on history had no co-morbidities. On renal biopsy, only a single core of tissue was submitted and sent for light microscopy. Histopathology did not receive any tissue specimens for immunofluorescence microscopy and electron microscopy. LM findings of the renal biopsy were in keeping with an immune-complex mediated diffuse proliferative

glomerulonephritis with a membranoproliferative reaction pattern, typical for the diagnosis of MPGN. As specimens for IFM were however not submitted it was difficult to distinguish between MPGN type I and type III.

He was started on cyclophosphamide and oral prednisone and his GFR increased to 63mL/min (previously it was 32mL/min. He developed *Escherichia coli* sepsis after the cyclophosphamide dose. He improved on antibiotics and was discharged home. Two months later, on admission for the second cycle of cyclophosphamide, his GFR had decreased again now to 31mL/min and he presented with anasarca, seizures and pulmonary oedema. He was started on renal replacement therapy, which was stopped just prior to discharge as his renal function had again improved after the cyclophosphamide was given. A few months later he suddenly demised. Unfortunately no documents could be traced regarding the events leading up to his death. However, after discussion with his relatives, myocardial infarction seems the most likely cause of his death.

Three other family members (102; 201; 202; 305) demised from renal disease in their fourth decade of life. Although the formal diagnosis is unknown, based on the history described by family members, MPGN is suspected.

The inheritance pattern does not appear to be a clear Mendelian pattern. The two brothers were from a consanguineous marriage that would suggest autosomal recessive, however more male family members are affected which would suggest x-linked recessive, but that does not account for the female family members. Also in other consanguineous marriages,

no siblings were affected. This suggests while there is a definite underlying genetic basis, it is either autosomal recessive with incomplete penetrance or multigenic.

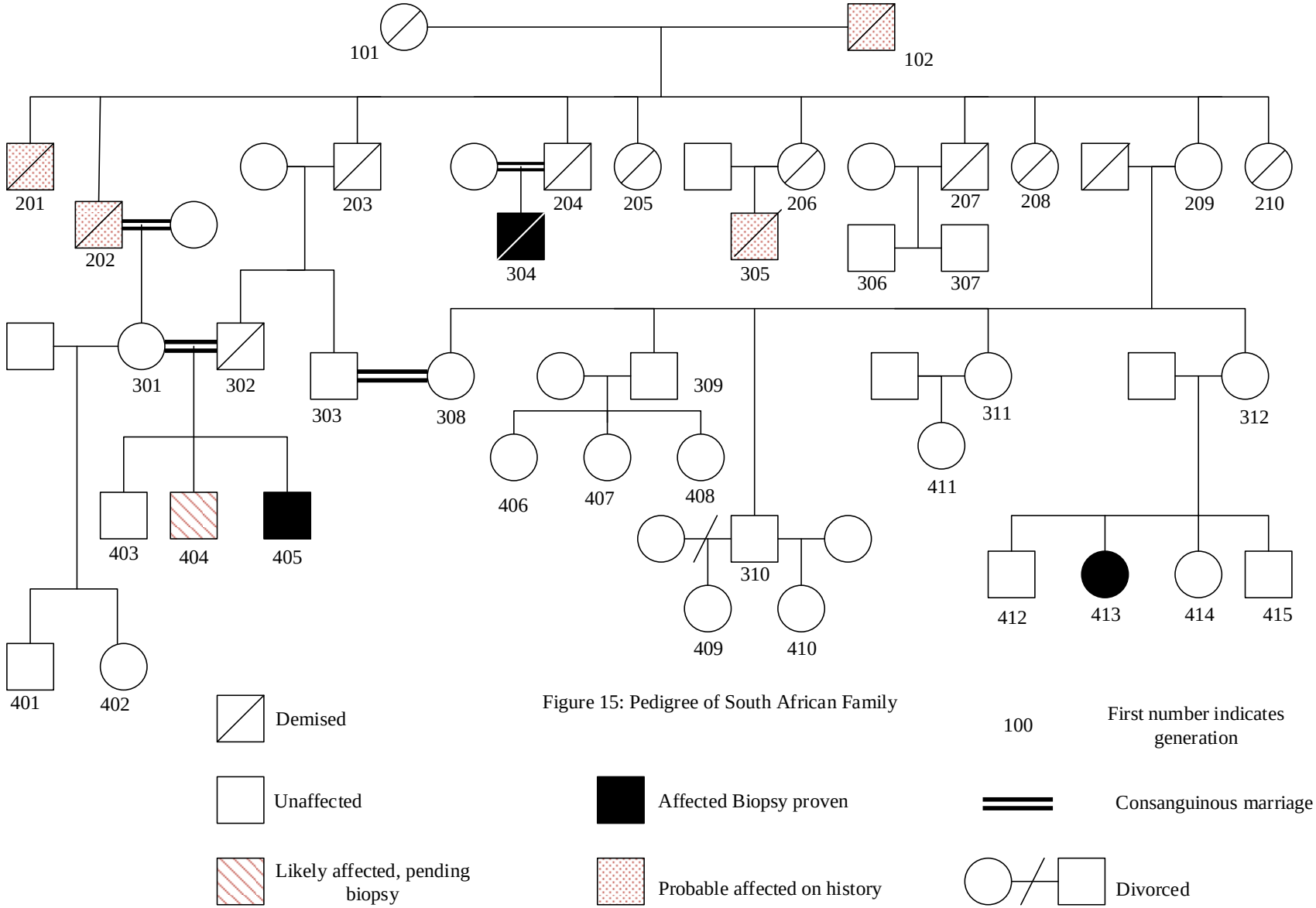


Figure 15: Pedigree of South African Family

Systematic review Results

The nine reports contained information regarding twelve families that combined with this study's family takes the number to thirteen families with thirty-four family members. There is a definite male predominance with twenty-five being male and only nine being female. The mean age was fifteen years, with a median of fourteen years and a mode of ten years at diagnosis. The eldest family member was fifty-one years at diagnosis. The age range was forty-eight years with a standard deviation of nine years. Table 4 contains the demographics of the family members. The mean follow up was six years. The mean creatinine at diagnosis was 134umol/L with a median of 66umol/L and a mode of 53umol/L. The mean age at which ESRD occurred was twenty-three years, with a median and mode of twenty-one years. The clinical presentation was mainly that of nephrotic syndrome with hypertension and proteinuria (table 5).

Table 7 contains the biopsy results and the previous MPGN classification as well as the new classification. In those family members where immunofluorescence was not performed, the same classification was given as the other members of their family. From this, it is noted that two distinct groups form; one that is complement-mediated and the other that is immune complex mediated, which the South African family falls into. The two groups are split from this point on. The studies by Sherwood et al. and Abderrahim et al. have too little information to be able to reclassify these families and thus they are not in the subdivided groups of immune complex mediated and complement-mediated.

Table 4: Demographics

Author Reference	Patient Designation	Gender	Age at Diagnosis (years)	Follow up (years)	Age at ESRD (years)
Berry et al. (11)	JM	Male	10	5	No
Berry et al.	PM	Female	9	2	No
Berry et al.	WG	Male	5	4	No
Berry et al.	KG	Male	7	5	No
Strutchfield et al. (13)	LA	Male	1yr 9months	2	No
Strutchfield et al.	NH	Male	1yr 5 months	6	5 Demised
Sherwood et al.	Father	Male	22	8	30
Sherwood et al.	Son	Male	4	1	NR
Abderrahim et al.	HI	Male	17	2	No
Abderrahim et al.	HA	Male	18	3	21
Bakkaloglu et al.	SG	Male	3	1	NR
Bakkaloglu et al.	AG	Male	10	7	10
Bakkaloglu et al.	BG	Male	3	6	NR
Bakkaloglu et al.	IG	Male	10	1	NR
Bakkaloglu et al.	MY	Male	9	4	NR
Bakkaloglu et al.	FY	Male	13	2	NR
Bogdanovic et al.	SC	Male	5	5.5	No
Bogdanovic et al.	MC	Female	5 yr. 6 months	3	8.5
Motoyama et al.	Case 1	Female	14	1	NR
Motoyama et al.	Case 2	Female	9	31	NR
Redahan et al.	1A	Female	16	22	21
Redahan et al.	1B	Male	18	13	21
Redahan et al.	2A	Male	22	2	23
Redahan et al.	2B	Male	15	2	17
This Report	304	Male	29	1	29 Demised
This Report	405	Male	15	8	19
This Report	404	Male	18	5	No
This Report	413*	Female	13	8	No
Neary et al.	213	Male	4	NR	10
Neary et al.	105	Male	51	NR	No
Neary et al.	212	Male	28	NR	No
Neary et al.	214	Female	21	NR	No
Neary et al.	103	Female	25	NR	54
Neary et al.	223	Female	16	NR	No
Mean			15	6	23
Median			14	4	21
Mode			10	2	21
Standard Deviation			9,85	6,77	12,51

Table containing the demographics of all affected family members:
ESRD: End Stage Renal Disease * Index patient

Table 5: Clinical presentation

Author Reference	Patient Designation	Hypertension	Haematuria	Proteinuria
Berry et al.	JM	Yes	Yes	Yes
Berry et al.	PM	Yes	Yes	Yes
Berry et al.	WG	Yes	No	Yes
Berry et al.	KG	Yes	No	Yes
Strutchfield et al.	LA	No	No	Yes
Strutchfield et al.	NH	No	Yes	Yes
Sherwood et al.	Father	Yes	NR	Yes
Sherwood et al.	Son	No	Yes	Yes
Abderrahim et al.	HI	Yes	Yes	Yes
Abderrahim et al.	HA	Yes	Yes	Yes
Bakkaloglu et al.	SG	Yes	NR	Yes
Bakkaloglu et al.	AG	Yes	NR	Yes
Bakkaloglu et al.	BG	No	NR	Yes
Bakkaloglu et al.	IG	No	NR	Yes
Bakkaloglu et al.	MY	Yes	NR	Yes
Bakkaloglu et al.	FY	Yes	NR	Yes
Bogdanovic et al.	SC	Yes	Yes	Yes
Bogdanovic et al.	MC	No	Yes	Yes
Motoyama et al.	Case 1	No	Yes	Yes
Motoyama et al.	Case 2	Yes	Yes	Yes
Redahan et al.	1A	NR	NR	NR
Redahan et al.	1B	NR	NR	NR
Redahan et al.	2A	Yes	Yes	Yes
Redahan et al.	2B	NR	NR	NR
This Report	304	Yes	Yes	Yes
This Report	405	No	Yes	Yes
This Report	404	No	Yes	Yes
This Report	413*	Yes	Yes	Yes
Neary et al.	213	Yes	No	Yes
Neary et al.	105	Yes	Yes	Yes
Neary et al.	212	Yes	Yes	Yes
Neary et al.	214	No	Yes	Yes
Neary et al.	103	Yes	NR	Yes
Neary et al.	223	Yes	Yes	Yes

Table depicting the clinical presentation of all the family members
* Index patient

Table 6: Laboratory Data

Author Reference	Patient Designation	Serum Creatinine umol/l	Serum Albumin g/l	Serum C3	Serum C4	GFR at diagnosis
Berry et al.	JM	27	18	Decreased	NR	NR
Berry et al.	PM	248	15	Decreased	NR	NR
Berry et al.	WG	44	28	Normal	Normal	NR
Berry et al.	KG	159	30	Normal	Normal	NR
Strutchfield et al.	LA	41	31	Normal	NR	76
Strutchfield et al.	NH	40	24	Normal	NR	77
Sherwood et al.	Father	NR	NR	NR	NR	NR
Sherwood et al.	Son	96	NR	Normal	Normal	140
Abderrahim et al.	HI	142	20	Normal	Normal	NR
Abderrahim et al.	HA	230	NR	Normal	Normal	NR
Bakkaloglu et al.	SG	53	22	Normal	Normal	Demised
Bakkaloglu et al.	AG	265	25	Normal	Normal	NR
Bakkaloglu et al.	BG	53	25	Normal	Normal	NR
Bakkaloglu et al.	IG	53	24	Normal	Normal	NR
Bakkaloglu et al.	MY	796	26	Decreased	Decreased	NR
Bakkaloglu et al.	FY	177	24	Decreased	Decreased	NR
Bogdanovic et al.	SC	35	13	Decreased	Decreased	147
Bogdanovic et al.	MC	62	23	Normal	Normal	145
Motoyama et al.	Case 1	62	45	Decreased	Normal	NR
Motoyama et al.	Case 2	62	29	Decreased	Decreased	NR
Redahan et al.	1A	NR	NR	NR	NR	NR
Redahan et al.	1B	NR	NR	NR	NR	NR
Redahan et al.	2A	NR	NR	Decreased	Decreased	NR
Redahan et al.	2B	NR	NR	NR	NR	NR
This Report	304	238	16	Normal	Normal	27
This Report	405	97	34	Normal	Normal	71
This Report	404	71	14	Normal	Normal	128
This Report	413*	39	26	Normal	Normal	182
Neary et al.	213	NR	21	Decreased	Normal	NR
Neary et al.	105	133	33	Normal	Normal	NR
Neary et al.	212	NR	26	Normal	Normal	NR
Neary et al.	214	NR	28	Normal	Normal	NR
Neary et al.	103	NR	30	Normal	Normal	NR
Neary et al.	223	NR	40	Normal	Normal	NR
Mean		134	21			
Median		66	21			
Mode		53,04	Not Calculated			
Standard Deviation		159,92	7,48			

Table depicting the laboratory data of all the family members
NR: Not recorded; * Index patient

Table 7: Biopsy Results

Author Reference	Patient Designation	Previous classification	IFM IgG	IFM IgM	IFM C3	New Classification
Berry et al.	JM	3	Yes low	Yes	Yes	CM
Berry et al.	PM	1	Yes low	Yes	Yes	CM
Berry et al.	WG	1	Yes	Yes	Yes	IM
Berry et al.	KG	1	Yes	Yes	Yes	IM
Strutchfield et al.	LA	1	Yes	Yes	Yes	IM
Strutchfield et al.	NH	1	Not done	Not done	Not done	IM
Sherwood et al.	Father	1	Not done	Not done	Not done	?
Sherwood et al.	Son	1	No	No	No	?
Abderrahim et al.	HI	1	Not done	Not done	Not done	?
Abderrahim et al.	HA	1	Not done	Not done	Not done	?
Bakkaloglu et al.	SG	1	NR	NR	NR	CM
Bakkaloglu et al.	AG	1	NR	NR	NR	CM
Bakkaloglu et al.	BG	1	NR	Yes	Yes	CM
Bakkaloglu et al.	IG	1	NR	Yes	Yes	CM
Bakkaloglu et al.	MY	1	NR	NR	Yes	CM
Bakkaloglu et al.	FY	1	NR	NR	Yes	CM
Bogdanovic et al.	SC	1	Yes	Yes	Yes	IM
Bogdanovic et al.	MC	3	Yes	Yes	Yes	IM
Motoyama et al.	Case 1	1	No	No	Yes	CM
Motoyama et al.	Case 2	1	No	No	Yes	CM
Redahan et al.	1A	1	Yes	Yes	No	IM
Redahan et al.	1B	NS	Yes	Yes	No	IM
Redahan et al.	2A	1	Yes	Yes	Yes	IM
Redahan et al.	2B	1	Yes	Yes	Yes	IM
This Report	304	1	Not done	Not done	Not done	IM on LM
This Report	405	1	Yes	Yes	Yes	IM
This Report	404	1	No	No	No	ATN
This Report	413*	1	Yes	No	Yes	IM
Neary et al.	213	3	No	No	Yes	CM
Neary et al.	105	3	No	No	Yes	CM
Neary et al.	212	3	No	No	Yes	CM
Neary et al.	214	3	No	No	Yes	CM
Neary et al.	103	3	NR	NR	NR	CM
Neary et al.	223	3	No	No	Yes	CM

Table containing the biopsy results of affected family members
IFM: Immunofluorescence microscopy; CM: Complement mediated; IM: Immune complex Mediated; ATN: Acute tubular necrosis; ? Not enough information supplied for classification. * Index patient

Fourteen family members were included in the IM group from five reports. The mean and median age of diagnosis, of the family members in the IM group was 15 years. The mean follow up was six years. Most of the patients presented with proteinuria but quite a few studies did not go into detail regarding the clinical presentation. One report (Redahan et al.) did not include any information regarding the laboratory data. (16) The other patients, however, had a mean serum creatinine of 83umol/L and a mean serum albumin of 24g/L. The mean age of ESRD was twenty years. Due to the small numbers, very little data is available to carry out a statistical analysis. The South African family is the largest family of affected family members in the immune-complex mediated group.

Table 8: Immune complex mediated MPGN demographics

Author Reference	Patient Designation	Gender	Age at Diagnosis (years)	Follow up (years)	Previous MPGN	New Classification
Berry et al.	WG	Male	5	4	1	IM
Berry et al.	KG	Male	7	5	1	IM
Strutchfield et al.	LA	Male	1	2	1	IM
Strutchfield et al.	NH	Male	1	5	1	IM
Bogdanovic et al.	SC	Male	5	5	1	IM
Bogdanovic et al.	MC	Female	5	3	3	IM
Redahan et al.	1A	Female	16	22	1	IM
Redahan et al.	1B	Male	18	13	NS	IM
Redahan et al.	2A	Male	22	2	1	IM
Redahan et al.	2B	Male	15	2	1	IM
This Report	304	Male	29	1	1	IM
This Report	405	Male	15	8	1	IM
This Report	404	Male	18	5	ATN	ATN
This Report	413*	Female	13	8	1	IM
Mean			15	6		
Median			15	5		
Mode			5	2		
Standard Deviation			7,29	5,78		

Table containing the demographics for the family members with immune complex mediated MPGN
NS: Not specified; ATN: Acute Tubular Necrosis; IM: immune complex mediated; * Index patient

Table 9: Immune mediated clinical presentation and residual findings							
Author Reference	Patient Designation	Hypertension	Persistant HTN	Haematuria	Persistant Haematuria	Proteinuria	Persistant Proteinuria
Berry et al.	WG	Yes	Yes	No	No	Yes	NR
Berry et al.	KG	Yes	Yes	No	No	Yes	NR
Strutchfield et al.	LA	No	Yes	No	NR	Yes	Yes
Strutchfield et al.	NH	No	Yes	Yes	NR	Yes	Yes
Bogdanovic et al.	SC	Yes	No	Yes	No	Yes	Yes
Bogdanovic et al.	MC	No	Yes	Yes	Yes	Yes	Yes
Redahan et al.	1A	NR	NR	NR	NR	NR	NR
Redahan et al.	1B	NR	NR	NR	NR	NR	NR
Redahan et al.	2A	Yes	NR	Yes	NR	Yes	NR
Redahan et al.	2B	NR	NR	NR	NR	NR	NR
This Report	304	Yes	Yes	Yes	Yes	Yes	Yes
This Report	405	No	Yes	Yes	Yes	Yes	Yes
This Report	404	No	No	Yes	Yes	Yes	Yes
This Report	413*	Yes	Yes	Yes	Yes	Yes	Yes
Table containing the clinical presentation and residual clinical features on the family members affected by immune complex mediated MPGN; * Index patient							

Table 10: Immune mediated laboratory data					
Author Reference	Patient Designation	Serum Creatinine umol/l	Serum Albumin g/l	Serum C3	Serum C4
Berry et al.	WG	44	28	Normal	Normal
Berry et al.	KG	159	30	Normal	Normal
Strutchfield et al.	LA	41	31	Normal	NR
Strutchfield et al.	NH	40	24	Normal	NR
Bogdanovic et al.	SC	35	13	Decreased	Decreased
Bogdanovic et al.	MC	61	23	Normal	Normal
Redahan et al.	1A	NR	NR	NR	NR
Redahan et al.	1B	NR	NR	NR	NR
Redahan et al.	2A	NR	NR	Decreased	Decreased
Redahan et al.	2B	NR	NR	NR	NR
This Report	304	238	16	Normal	Normal
This Report	405	97	34	Normal	Normal
This Report	404	71	14	Normal	Normal
This Report	413*	39	26	Normal	Normal
Mean		83	24		
Median		53	25		
Mode		Not Calculated	Not Calculated		
Standard Deviation		66,61	7,39		
Table containing the laboratory data on the family members affected by immune complex mediated MPGN; * Index patient					

Table 11: ESRD and Inheritance Pattern			
Author Reference	Patient Designation	Age at ESRD (years)	Inheritance Pattern
Berry et al.	WG	Not by follow up	Multigenic/ X-linked
Berry et al.	KG	Not by follow up	Multigenic/ X-linked
Strutchfield et al.	LA	Not by follow up	X-linked Recessive
Strutchfield et al.	NH	5 Demised	X-linked Recessive
Bogdanovic et al.	SC	Not by Follow Up	Multigenic
Bogdanovic et al.	MC	8.5	Multigenic
Redahan et al.	1A	21	Autosomal Recessive
Redahan et al.	1B	21	Autosomal Recessive
Redahan et al.	2A	23	Autosomal Recessive/ X-linked
Redahan et al.	2B	17	Autosomal Recessive/ X-linked
This Report	304	Demised before ESRD occurred	Multigenic
This Report	405	19	Multigenic
This Report	404	Not by follow up	Multigenic
This Report	413*	Not by follow up	Multigenic
Mean		20	
Median		21	
Mode		21	
Standard Deviation		2,28	

Table containing the age at which end stage renal disease (ESRD) occurred in family members affected by immune complex mediated MPGN and the family inheritance patterns suggested by studies; * Index patient

The complement- mediated families consisted of sixteen family members, had a mean age at diagnosis of fifteen years with a mean follow up period of six years (table 12). Almost half of the family members in this group had a previous diagnosis of MPGN type III compared to only one family member in the immune complex mediated group.

Most of the family members presented with hypertension and proteinuria (table 13) and more family members had a decreased serum complement, 41% versus 14% in the immune mediated group (table 14). There are marked variations in the serum creatinine results, due to some family members presenting late or some had been previously diagnosed at other hospitals and their results at diagnosis were not available, hence the large standard deviation for the serum creatinine.

Only three patients had ESRD by the time the reports were written and their ages fluctuated from 10 to 54 years, with a mean disease duration of twelve years. With regards to the inheritance pattern, there again is a marked variance but autosomal dominance occurs more frequently, however that is mainly due to the study by Neary et al. which had six family members (table 15) of the total sixteen family members.

Table 12: Complement mediated demographics						
Author Reference	Patient Designation	Gender	Age at Diagnosis (years)	Follow up (years)	Previous MPGN	New Classification
Berry et al.	JM	Male	10	5	3	CM
Berry et al.	PM	Female	9	2	1	CM
Bakkaloglu et al.	SG	Male	3	1	1	CM
Bakkaloglu et al.	AG	Male	10	7	1	CM
Bakkaloglu et al.	BG	Male	3	6	1	CM
Bakkaloglu et al.	IG	Male	10	1	1	CM
Bakkaloglu et al.	MY	Male	9	4	1	CM
Bakkaloglu et al.	FY	Male	13	2	1	CM
Motoyama et al.	Case 1	Female	14	1	1	CM
Motoyama et al.	Case 2	Female	9	31	1	CM
Neary et al.	213	Male	4	NR	3	CM
Neary et al.	105	Male	51	NR	3	CM
Neary et al.	212	Male	28	NR	3	CM
Neary et al.	214	Female	21	NR	3	CM
Neary et al.	103	Female	25	NR	3	CM
Neary et al.	223	Female	16	NR	3	CM
Mean			15	6		
Median			10	3		
Mode			10	2		
Standard Deviation			12,10	9,04		

Table containing the demographics for the family members with complement mediated MPGN
CM: complement mediated MPGN; NR: Not recorded

Table 13: Complement mediated clinical presentation

Author Reference	Patient Designation	Hypertension	Residual Hypertension	Haematuria	Persistant Haematuria	Proteinuria	Persistant Proteinuria
Berry et al.	JM	Yes	NR	Yes	Yes	Yes	NR
Berry et al.	PM	Yes	NR	Yes	Yes	Yes	NR
Bakkaloglu et al.	SG	Yes	NR	NR	NR	Yes	NR
Bakkaloglu et al.	AG	Yes	NR	NR	NR	Yes	NR
Bakkaloglu et al.	BG	No	Yes	NR	NR	Yes	No
Bakkaloglu et al.	IG	No	Yes	NR	NR	Yes	No
Bakkaloglu et al.	MY	Yes	Yes	NR	NR	Yes	Yes
Bakkaloglu et al.	FY	Yes	No	NR	NR	Yes	No
Motoyama et al.	Case 1	No	No	Yes	Yes	Yes	No
Motoyama et al.	Case 2	Yes	No	Yes	No	Yes	Yes
Neary et al.	213	Yes	NR	No	NR	Yes	Yes
Neary et al.	105	Yes	NR	Yes	NR	Yes	Yes
Neary et al.	212	Yes	NR	Yes	NR	Yes	NR
Neary et al.	214	No	NR	Yes	NR	Yes	NR
Neary et al.	103	Yes	NR	NR	NR	Yes	NR
Neary et al.	223	Yes	NR	Yes	NR	Yes	NR

Table containing the clinical presentation and residual clinical features on the family members affected by complement mediated MPGN

Table 14: Complement mediated laboratory data					
Author Reference	Patient Designation	Serum Creatinine umol/l	Serum Albumin g/l	Serum C3	Serum C4
Berry et al.	JM	26	18	Decreased	NR
Berry et al.	PM	247	15	Decreased	NR
Bakkaloglu et al.	SG	22	Normal	Normal	Demised
Bakkaloglu et al.	AG	25	Normal	Normal	CRF
Bakkaloglu et al.	BG	25	Normal	Normal	NR
Bakkaloglu et al.	IG	24	Normal	Normal	NR
Bakkaloglu et al.	MY	795	26	Decreased	Decreased
Bakkaloglu et al.	FY	176	24	Decreased	Decreased
Motoyama et al.	Case 1	62	45	Decreased	Normal
Motoyama et al.	Case 2	62	29	Decreased	Decreased
Neary et al.	213	NR	21	Decreased	Normal
Neary et al.	105	133	33	Normal	Normal
Neary et al.	212	NR	26	Normal	Normal
Neary et al.	214	NR	28	Normal	Normal
Neary et al.	103	NR	30	Normal	Normal
Neary et al.	223	NR	40	Normal	Normal
Mean		175	27		
Median		62	26		
Mode		53	26		
Standard Deviation		221,78	7,56		
Table containing the laboratory data on the family members affected by complement mediated MPGN. NR: Not Recorded					

Table 15: Complement mediated age of ESRD and inheritance patterns			
Author Reference	Patient Designation	Age at ESRD	Inheritance Pattern
Berry et al.	JM	Not by follow up	Multigenic
Berry et al.	PM	Not by follow up	Multigenic
Bakkaloglu et al.	SG	NR	Autosomal Dominant/ X-linked with incomplete penetrance
Bakkaloglu et al.	AG	10	Autosomal Dominant/ X-linked with incomplete penetrance
Bakkaloglu et al.	BG	NR	Autosomal Dominant/ X-linked with incomplete penetrance
Bakkaloglu et al.	IG	NR	Autosomal Dominant/ X-linked with incomplete penetrance
Bakkaloglu et al.	MY	NR	Autosomal Dominant/ X-linked with incomplete penetrance
Bakkaloglu et al.	FY	NR	Autosomal Dominant/ X-linked with incomplete penetrance
Motoyama et al.	Case 1	NR	Unclear
Motoyama et al.	Case 2	NR	Unclear
Neary et al.	213	10	Autosomal Dominant
Neary et al.	105	Not by follow up	Autosomal Dominant
Neary et al.	212	Not by follow up	Autosomal Dominant
Neary et al.	214	Not by follow up	Autosomal Dominant
Neary et al.	103	54	Autosomal Dominant
Neary et al.	223	Not by follow up	Autosomal Dominant

Table containing the age at which end stage renal disease (ESRD) occurred in family members affected by complement mediated MPGN and the family inheritance patterns suggested by studies. NR: Not Recorded

DISCUSSION

Redahan et al suggested that complement dysregulation played an important "role in the pathogenesis of immune complex mediated MPGN" as evidenced by the following (16) :

- Familial cases of type II MPGN have been found to have mutations in complement factors and in complement factor proteins resulting in dysregulation of the complement cascade resulting in disease. (16)
- The study by Neary et al found a link between chromosome 1q, a locus containing multiple genes for factors affecting the complement cascade. (4)
- A previous cohort of MPGN type I patients with both immunoglobulins and complement staining on IFM were found to have mutations in complement factor H (10, 4%) and complement factor I (6, 2%), suggesting dysregulation of the alternative pathway of the complement cascade. (19)

This however does not explain why certain family members are affected, particularly in families with consanguineous marriages. Nor does it account for the other 83, 6% of people with MPGN type I. The study by Servais et al. also did not look into the underlying cause of MPGN (19) was it caused by autoimmune diseases and of those diseases, which ones are affected by abnormal alternative pathway of complement? Thus, do those results apply to familial MPGN? While the above is useful in giving possible genes to look at in the future, more work needs to be done in this field.

By doing the systematic review, it is clear that there are two forms of familial MPGN, namely the complement mediated and the immune complex mediated MPGN. Therefore, the current classification of MPGN needs to change and a fourth category added to the immune complex mediated group, that of familial or inherited immune complex-mediated MPGN, as the current classification only includes familial MPGN in the complement

mediated group. By splitting the two groups up into their pathogenesis, hopefully more information will be obtained in the future as to the underlying cause, particularly for the immune complex-mediated MPGN.

The limitations of the Systematic review were:

- Some studies did not contain all the information pertaining to their patients especially information regarding the biopsy specimens.
- As well, some patients were diagnosed at other hospitals and their original results were not available.
- The late presentation of some patients due to lack of funding.
- Small cohort of patients.

Despite the small cohort of patients, important data has been obtained particularly for future patients diagnosed with familial MPGN and their family members, as it provides evidence to promote the active work up of all family members under the age of 20 years, as the disease is rapidly progressive. Furthermore patients diagnosed with idiopathic immune complex mediated MPGN marked efforts should be directed to identify possible affected family members.

Furthermore, this is the first study to assess a family in South Africa affected with familial MPGN of the immune-mediated type. It is also the largest cohort of family members affected by immune-mediated MPGN. By further studying this family, particularly with regards to an underlying genetic basis of their disease, more information will be gained to assist other families affected.

CONCLUSIONS

Through the study and case report of this South African family with multiple members affected by familial MPGN as well as the systematic review of available studies of families affected by familial MPGN the following conclusions can be drawn:

1. The underlying inheritance pattern for the South African family is possibly multigenic or autosomal recessive with incomplete penetrance.
2. The current classification of immune complex-mediated MPGN needs to be modified to include an inherited form.
3. A follow up study is required on the South African family to assess the possible underlying genetic basis of their disease.
4. Lastly, an international collaboration is required to further study this disease due to the limited number of families affected worldwide.

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APPENDICES