Original Article

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Pathology Section

Clinicopathological Profile of IgA Nephropathy: A Study of Tertiary Care Centre in Northern India

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ABSTRACT

Introduction: Immunoglobulin A Nephropathy (IgAN) is the most common Glomerulonephritis (GN) in the world which mainly occurs in the males of 30-40 years of age, following infections like tonsillitis, pharyngitis, pneumonia and Urinary Tract Infection (UTI). It presents with proteinuria, haematuria, hypertension, nephrotic syndrome, nephritic syndrome, acute renal failure and chronic renal failure. Immunofluorescence (IF) positivity is a must for its diagnosis. It is also common in India but there are only few studies done so far, due to non-availability of IF technique.

Aim: To study the histopathological spectrum of IgAN and compared each with its clinical presentation.

Materials and Methods: This was a descriptive study, conducted on all renal biopsies diagnosed as primary IgAN over a period of six years and six months (retrospective period was from 1st October 2007 to 30th September 2012 and prospective period was from 1st October 2012 to 31st March 2014) in the Department of Pathology, Christian Medical College and Hospital, Ludhiana. Renal biopsies' sections of 3-4 µm thickness were made, stained with Hematoxylin and Eosin stain (H&E), Periodic Acid-Schiff (PAS), Masson's Trichrome and Silver Methanamine and studied under light microscope. The renal biopsies were evaluated under the fluorescent microscope to study the positivity for the IgA, IgM, IgG, and C3. The histopathological classification was done according to the Haas System. These findings were compared with the clinical presentations.

Results: Out of the 305 renal biopsies received, there were 60 (19.6%) cases diagnosed to have primary IgAN. The youngest patient aged two years and oldest patient aged 85 years. The mean age of presentation was 37.6 years. Majority, 16 (26.6%) of the patients were in the age group of 21-30 years. In all subclasses, there was a male preponderance with average male:female ratio of 3:1. Subclass V formed the largest group with 25 (41.67%) patients, which concludes that maximum patients came to hospital in a late stage.

Conclusion: IgAN is a common entity seen in Northern part of India. But since most of the patients are coming in the late stage, makes it a missed diagnosis in earlier stages. Uncommon direct IF technique in India adds to this problem. Hence, appropriate steps like renal biopsies and its IF should be taken in patients with persistent haematuria and proteinuria for early diagnosis and management of the most common cause of GN of the world.

Keywords: Haas classification, Immunofluorescence, Renal biopsy

INTRODUCTION

It was in the year 1968 when IgAN was identified as a distinct clinicoimmunological entity by Berger and Hinglais [1]. Since nothing much was known about it, so it was underestimated as a benign nephropathy for a long time. But several studies done thereafter revealed that IgAN although frequently takes benign course [2], is also one of the main cause of the End Stage Renal Disease (ESRD) among the primary glomerular diseases with majority of the patients progressing to chronic renal insufficiency, and then developing ESRD [3]. With the passage of time, IgAN had gained the popularity when it was observed that it is the most common GN in the world [4], with increasing incidence in India [5-7]. The pathogenesis of IgAN depends not only on the genetic factors but is also influenced by environmental factors, making its immunopathogenesis as a multi-hit process [8]. Deposits predominantly comprising of IgA along with IgG, IgM, or both in the mesangium is the diagnostic hallmark of IgAN. Different studies reveal the frequency of IgA without IgG or IgM from 0 to 85% [9,10]. Involvement of the alternative and lectin pathways of complement activation is supported by presence of complement C3 and properdin in most of the cases and frequent presence of complement C4 or C4d, mannose-binding lectin and terminal complement complex (C5b–C9). Complement C1q is usually absent. A biochemical feature of central importance in the pathogenesis of IgAN is presence of mesangial IgA, exclusively of the IgA1 subclass, which is deficient in galactose [11]. The histological features of IgAN vary greatly not only among patients, but also within the individual biopsy. The common ones are increase in mesangial matrix and hypercellularity and other uncommon glomerular lesions are segmental scarring, focal necrosis, and crescents in Bowman's space [12]. Electron Microscopy (EM) usually shows electron-dense material corresponding to immune deposits on IF microscopy. These are generally observed in mesangial and paramesangial areas but are occasionally present in subepithelial and subendothelial portions of Glomerular Basement Membranes (GBM) [9]. As far as the clinical features are concerned, it is had been observed that IgAN occur most commonly in males between the ages of 30-40 years [13,14]. The major clinical presentations of IgAN are: asymptomatic urinary abnormalities (proteinuria), macroscopic haematuria, hypertension, nephrotic syndrome, nephritic syndrome, acute and chronic renal failure [15]. It frequently occurs one or two days after infectious illness mainly pharyngitis or tonsillitis, but may also occur following gastroenteritis, pneumonia or UTI [16,17].

Histological grading, nephrotic range proteinuria, decreased Glomerular Filtration Rate (GFR), and hypertension are robust predictors of adverse renal outcomes in IgAN [18]. Cattran DC et al., have developed the Oxford classification of IgAN to standardise the grading of features on LM [19]. Earlier, Haas M et al., had classified IgAN into five subclasses which will be followed in this study [17]. These are summarised as follows: Subclass I is minimal histologic lesion, subclass II histologically resembling focal segmental glomerulosclerosis, subclass III have features of focal

proliferative GN, subclass IV show features of diffuse proliferative GN and subclass V is advanced chronic GN. The clinical condition deteriorates with increase in subclass. The main objective of the study was to know the incidence of IgAN in this part of India and correlating its pathological severity with clinical presentations, so as to evaluate the importance of routine IF technique in evaluating the renal diseases even in developing parts of the world. It can also help different studies in evaluating the underlying factors which can help in treating the disease.

MATERIALS AND METHODS

This was a descriptive study, conducted in Christian Medical College and Hospital, Ludhiana on all patients whose renal biopsies were received in the Department of Pathology and diagnosed as IgAN over a period of six and half years, five years of retrospective study (October 2007 to September 2012) and one and half years of prospective study (October 2012 to March 2014).

Inclusion criteria: Confirmation by immunofluorescence of positivity for IgA antisera, with IgA being the dominant or the co-dominant Ig deposited.

Exclusion criteria: Exclusion of other systemic diseases which can affect/alter the morphology- for example, diabetes mellitus. Exclusion of secondary causes of IgAN, such as liver diseases or Henoch-Schönlein Purpura Nephritis (HSPN)

Patients' data: For each patient, basic epidemiological data, relevant signs and symptoms, and laboratory investigations were collected from the files from medical records for the retrospective cases and from the biopsy forms of the prospective cases, as per the protocol.

Evaluation of biopsies: The renal biopsy specimen obtained, were immediately fixed in 10% neutral buffered formalin for histopathological examination and in transport media for IF.

The biopsies were assigned identification numbers. Thin sections of 3-4 µm thickness were taken and slides were stained with Haematoxylin and Eosin (H&E), Periodic Acid Schiff (PAS), Silver Methenamine and Masson Trichrome (in selected cases only) and then used for histological grading.

The individual histological parameters were studied in detail, according to the guidelines of the Haas classification [17].

Direct IF technique was as per protocol followed at Department of Pathology, Christian Medical College and Hospital, Ludhiana which is a modification from Culling CFA et al., [20].

RESULTS

During the study period total 305 renal biopsies were received. Number of primary IgAN cases was 60 (19.6%). The range of age of patients with IgAN was 2-85 years, with mean age of 37.6 years. Age group of 21-30 years formed the largest group with 16 (26.6%) cases. Male: female ratio was 3:1. Among all the subclasses, subclass V had maximum cases, 25 (41.67%) which concludes that maximum patients came to hospital in a late stage [Table/Fig-1].

Age groups (Years)	No. of patients (%)	Male: Female ratio
0-10	4 (6.7)	-
11-20	6 (10)	5:1
21-30	16 (26.6)	4.3:1
31-40	9 (15)	3.5:1
41-50	7 (11.6)	6:1
51-60	11 (18.3)	1:1.2
61-70	6 (10)	2:1
71-80	-	-
81-90	1 (1.6)	-
Total cases	60 (100)	3:1

[Table/Fig-1]: Age and sex distribution of patients with IgAN.

The main clinical presentations were haematuria, proteinuria, oedema, hypertension with history of preceding infections (UTI/URTI/GIT), which are summarised as follows [Table/Fig-2]. It was observed that higher the subclass, severe were the symptoms, e.g., hypertension and deranged renal function was common in higher subclasses i.e., mainly IV and V as compared to lower subclasses i.e., I, II and III.

Clinical features	No. of patients (%) in different subclasses				
	I	II	III	IV	V
No of cases (%)	4 (6.6)	3 (5)	21 (35)	7 (11.6)	25 (41.6)
Age range (mean)	2-30 (21)	18-49 (29.7)	9-68 (34.9)	23-65 (45.3)	7-85 (41.4)
Male: female ratio	3:1	All males	2.5:1	6:1	2.5:1
Gross/ microscopic haematuria	3 (75%)	2 (66.6%)	16 (76.1%)	6 (85.7%)	18 (72%)
Proteinuria	4 (100%)	2 (66.6%)	20 (95.2%)	7 (100%)	22 (88%)
Oedema	3 (75%)	1 (33.3%)	13 (61.9%)	4 (57.1%)	12 (48%)
Hypertension	1 (25%)	1 (33.3%)	12 (57.1%)	5 (71.4%)	18 (72%)
History of preceding infections (UTI and GIT)	1 (25%)	None	15 (71.4%)	2 (28.5%)	10 (40%)
Serum creatinine	0.5-1.4 (0.9)	1.7-3.7 (2.4)	0.3-18.3 (2.6)	2.1-4.1 (3.1)	1.1-12.7 (4.0)
Blood urea	22-60 (39.5)	52-58 (55.5)	51-431 (79.5)	71-97 (81.1)	34-318 (99.3)

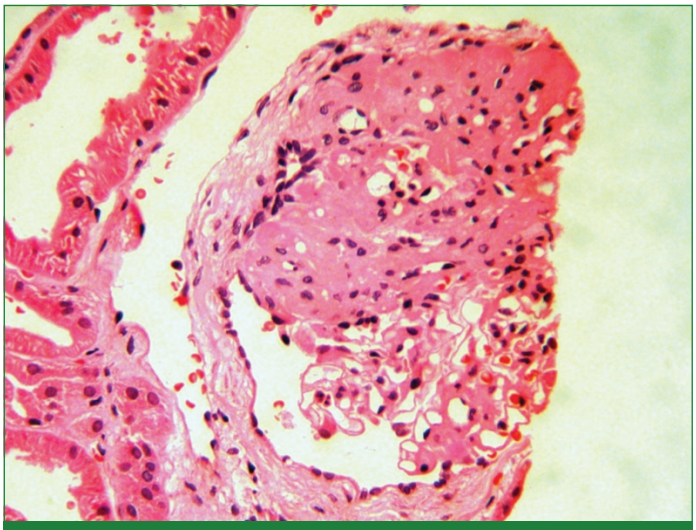
[Table/Fig-2]: Clinical presentation of patients in different subclasses.
UTI: Urinary tract infections; GIT: Gastrointestinal tract

Changes noted in renal biopsies of patients with primary IgAN according to Haas classification are summarised as follows, [Table/Fig-3], with increase in mesangial matrix as commonest in subclass I. Subclass II had both Focal segmental glomerulosclerosis (FSGS)

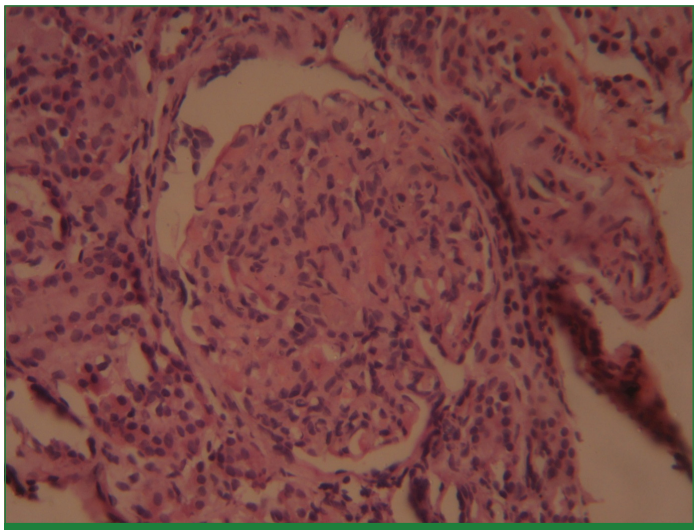
Histological features	No of cases (%) in different subclasses				
	I	II	III	IV	V
Glomerular changes					
Increase in mesangial matrix	4 (100%)	1 (33.3%)	7 (33.3%)	3 (42.8%)	5 (20%)
FSGS	-	3 (100%)	-	-	-
Mesangial hypercellularity	-	-	18 (85.7%)	7 (100%)	6 (24%)
Endocapillary proliferation	-	-	3 (14.2%)	-	3 (12%)
Crescents	-	-	6 (28.5%)	-	4 (16%)
Glomerular sclerosis	-	-	10 (47.6%)	3 (42.8%)	-
Synechiae	-	-	11 (52.3%)	5 (71.4%)	3 (12%)
Mesangiolysis	-	-	2 (9.5%)	1 (14.2%)	2 (8%)
Global sclerosis (>40% glomeruli)	-	-	-	-	19 (76%)
Glomerular atrophy	-	-	-	-	7 (28%)
Tubular changes					
Tubular atrophy					
Mild	2 (50%)	3 (100%)	6 (28.5%)	3 (42.8%)	
Moderate	-		2 (9.5%)		15 (60%)
Severe	-		-		
Tubular casts	3 (75%)		14 (66.6%)	4 (57.1%)	23 (92%)
Interistitial changes					
Inflammation	1 (25%)	2 (66.6%)	11 (52.3%)	3 (42.8%)	16 (64%)
Fibrosis	-	2 (66.6%)	3 (14.2%)	1 (14.2%)	17 (68%)
Blood vessels changes					
Hyaline arteriosclerosis	-	-	1 (4.7%)	4 (57.1%)	11 (44%)

[Table/Fig-3]: Histopathological findings of patients in different subclasses.
FSGS: Focal segmental glomerulosclerosis

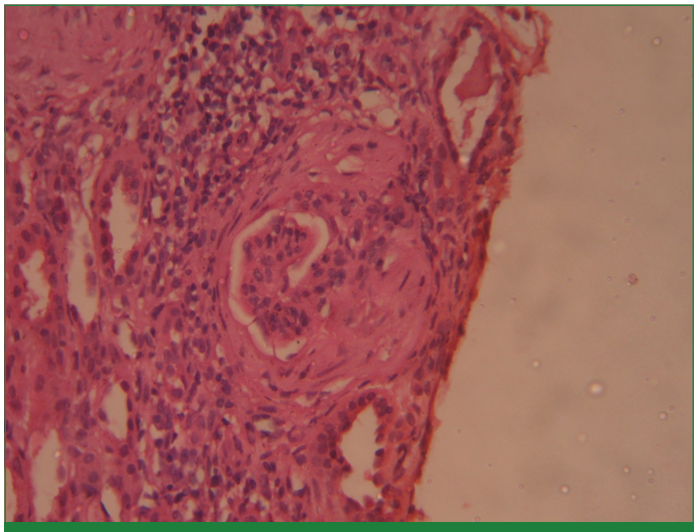
[Table/Fig-4], and increase in mesangial matrix. The higher subclass histological features including mesangial hypercellularity [Table/Fig-5], endocapillary proliferation, crescents [Table/Fig-6], global sclerosis [Table/Fig-7], synechiae and glomerular atrophy alongwith tubular atrophy [Table/Fig-8] were not seen in lower subclasses (I and II), depicting more renal damage in the higher subclasses and justifying the worse prognosis of same. Interstitial fibrosis were absent in class I and Interstitial inflammation is minimal in subclass I and II [Table/Fig-8]. Blood vessels had hyaline arteriosclerosis I subclass III to V [Table/Fig-9].



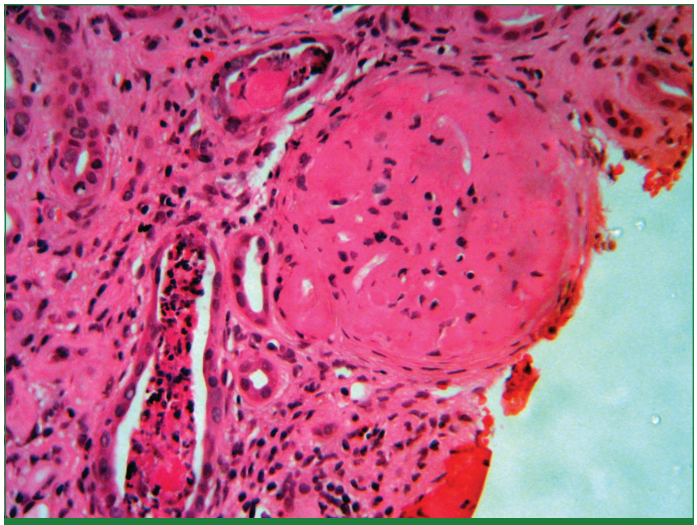
[Table/Fig-4]: Focal and segmental glomerular sclerosis- subclass II (H&E 400X).



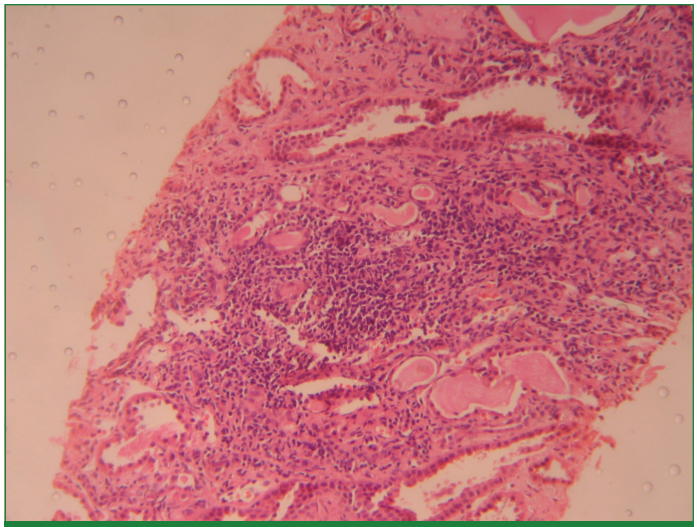
[Table/Fig-5]: Mesangial hypercellularity (H&E 400X).



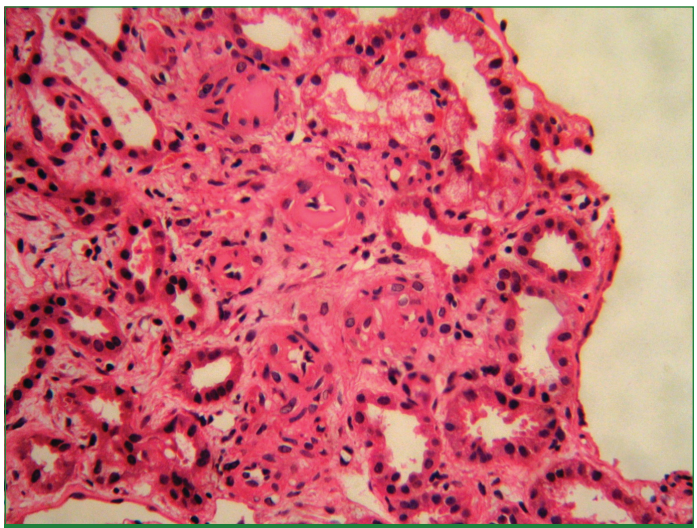
[Table/Fig-6]: Formation of crescents in the glomerulus (H&E 400X).



[Table/Fig-7]: Globally Sclerosed Glomerulous (GSG) and Wbcs cast (H&E 400X).



[Table/Fig-8]: Moderate tubular atrophy and moderate interstitial inflammation (H&E 200X).



[Table/Fig-9]: Hyaline arteriosclerosis (H&E 400X).

IF findings showed presence of mesangial and/or paramesangial IgA alone or with IgM/IgG/C3. Number of cases having different combinations of presence of Ig or complements are shown in [Table/Fig-10]. The intensity of IgA varies in different subclasses, e.g., in subclass I and II, all the cases had 2+ deposition of IgA in the mesangium, subclass III all cases had 3+ positivity for IgA in the mesangium with one case in addition showing capillary wall deposits. Subclass IV cases had the mesangial and mesangial with capillary wall IgA 2+ positivity {3 (42.8%) and one (14.2%) patients' renal biopsies, respectively}, mesangial IgA 3+ positivity was present in 2 (28.5%)

patients' renal biopsies and capillary wall 3+ IgA positivity was seen in one (14.2%). In subclass V mesangial and capillary wall 2+ IgA positivity was seen in 14 (56%) and 3 (12%) cases, respectively. In 3 (12%) cases IgA 2+ deposition was seen in mesangium as well as capillary wall. Mesangial and capillary wall 3+ positivity was present in 3 (12%) and one (4%) cases, respectively. Mesangial as well as capillary wall 3+ positivity was present in one (4%) case.

IF findings	No of cases (%)				
	Subclass I	Subclass II	Subclass III	Subclass IV	Subclass V
IgA only	1 (25)	-	6 (28.5)	-	4 (16)
IgA + C3	1 (25)	1 (33.3%)	3 (14.2)	1 (14.2)	4 (16)
IgA + IgM	-	1 (33.3%)	4 (19)	1 (14.2)	3 (12)
IgA + IgG + C3	-	-	-	-	1 (4)
IgA + IgM + C3	2 (50)	1 (33.3%)	6 (28.5)	5 (71.4)	13 (52)
IgA+ IgG+ IgM	-	-	2 (9.5)	-	

[Table/Fig-10]: Immunofluorescence findings of patients in all subclasses.

DISCUSSION

IgAN although being the most common GN in the world is not commonly studied in every part of India due to lack of IF technique. To fill this lacuna, this study was done to add on information in the present data of Indian IgAN burden of disease. The clinical predictors of IgAN as assessed by many studies which were significantly associated with dialysis/ESRD/death, are decreased estimated GFR (eGFR), proteinuria and hypertension along with histological grading [21]. This study showed 19.6% cases diagnosed to have primary IgAN however, it has been compared to prevalence of IgAN in different parts of world. It showed high prevalence of IgAN in Northern part of India (Punjab) which was comparable to Indian studies done by Chandrika BK, and Vanikar AV et al., with prevalence of 14.2% and 16.2%, respectively [5,22] and a Pakistani study [23] with prevalence of 12.6%, but much lower than a recent study done by Chowdry AM et al., [7], which reported prevalence of 42.8% in Kashmir (India). Some studies had prevalence even lower than our study ranging from 7.85% to 10.4% [6,14,24-27].

The prevalence was much lower than many other European countries like France [28] with prevalence of 33.4% and Asian countries, like, Japan [29] and China [30] with prevalence of 47.2% and 34.1% respectively, which might be because of renal biopsy and IF practices followed rather than actual burden of disease here.

The mean age of presentation of IgAN was 37.6 years in this study which was similar to many Indian as well as international studies [7, 25-28] with mean age ranging from 31-43 years. The study showed male predominance similar to many studies [7,25-28] with exception of studies by Li PK et al., and Prakash S et al., which had female predominance [31,32]. Distribution of the different subclasses was quite variable. Subclass V as the most common subclass as seen in this study was also observed by Chowdry AM et al., and Mittal N et al., [7,14]. Subclass III was the commonest finding in studies done by Haas M [17,33] and Siddappa S et al., [27]. Some studies observed subclass II as most common subclass [5,34]. The clinical presentations of IgAN are haematuria, hypertension, proteinuria, history of infections and renal failure. In this study, haematuria was the commonest presentation present in 45 (75%) cases. It was common in all the subclasses. Similar findings were noted by Haas M [17,33] and Mittal N et al., but study by Siddappa S et al., didn't find haematuria as that common in any of 5 subclasses [14,27].

Proteinuria, one of the adverse prognostic factors, was common in all subclasses in our study. Similar to this study, studies supporting this fact are mentioned herewith. In subclass I, all the patients had proteinuria but none of them showed nephrotic range proteinuria. Haas M et al., observed proteinuria was present in 4 (22%) patients with nephrotic range proteinuria absent in all adult patients [33]. But in paediatric population, the proteinuria was present in one (4%) patients with nephrotic range proteinuria absent in all.

In subclass II, the study found that 2 (66.6%) patients had proteinuria and both of them had it in the nephrotic range. Haas M et al., found the mean urinary protein was 5.5 g/24 hours [17]. Haas M et al., among adult patients observed the mean urinary protein was 5.6 gm/24 hours [33]. There were 100% (adult) patients who had proteinuria more than 1 gm/day but 75% patients had nephrotic range proteinuria. Among paediatric patients, 24 hours urinary protein excretion was 5.1 gm/24 hours. An 86% patients had proteinuria of more than 1 gm/day and 29% patients had >3 gm/day proteinuria. Siddappa S et al., observed mean proteinuria as 5.5 gm/day [27]. Mittal N et al., differs in having the mean proteinuria of 2.68 gm/24 hours [14].

In reference to subclass III, we observed 20 (95.2%) patients had proteinuria, out of which 10 (47.6%) patients having nephrotic range proteinuria. The mean proteinuria was 2.5 gm/24 hours as seen in study by Haas M et al., which was quite different from this study [17]. Haas M et al., in adults found proteinuria was present in 39 (74%) patients with nephrotic range proteinuria in 11 (21%) patients [33]. In paediatric patients, proteinuria was present in 15 (35%) patients with nephrotic range proteinuria in 2 (43%) patients. Mittal N et al., mean proteinuria level was 2.18 gm/24 hours and nephrotic range proteinuria was seen in 40% cases [14].

Subclass IV, proteinuria was seen in all the 7 (100%) patients and 2 (28.5%) patients had nephrotic range proteinuria in this study. Haas M et al., observed mean proteinuria as 3.8 gm/24 hours [17]. Haas M et al., among adult patients, found the mean urinary protein of 3.7 gm/24 hours [33]. There were 80% patients who had proteinuria more than 1 gm/day but 55% patients had nephrotic range proteinuria. Among paediatric patients, Haas M et al., found the 24 hours urinary protein excretion was 3.9 gm/24 hours, 90% patients had proteinuria of more than 1 gm/day and 40% patients had >3 gms/day proteinuria [33].

In subclass V, 22 (88%) patients had proteinuria and out of these, 3 (12%) had nephrotic range proteinuria Haas M et al., found the mean urinary protein was 4.6 gm/24 hours [17]. Haas M et al., among the adult population observed the mean proteinuria levels were 3.4 grams/24 hours [33]. Patients with proteinuria of >1 gm/day were 19 (95%) and of >3 gm/day were 13 (65%). In the paediatric population, the mean proteinuria was 5.4 gm/24 hours. All the patients had proteinuria of more than 3 gm/24 hours. Mittal N et al., observed the mean proteinuria level was 2.05 gm/24 hours and nephrotic range proteinuria was seen in 12.2% cases [14].

Another important factor required to be considered is hypertension. In subclass I, II, III, IV and V hypertension was present in 25%, 33.3%, 57.1%, 71.4% and 72% patients in this study; in 33%, 25%, 39%, 66% and 90% patients, respectively in study by Haas M et al., in 11%, 17%, 42%, 81% and 95% patients in study by Haas M et al., [17,33]. Siddappa S et al., observed 33.3%, 45.5%, 62.5%, 57.1% patients having hypertension in subclass II, III, IV and V, respectively [27]. Mittal N et al., found hypertension in 50%, 75%, 85.7%, in subclass II, III and V respectively [14]. All these studies as present study support proteinuria and hypertension as bad prognostic signs in progression of IgAN.

Limitation(s)

This study is a hospital-based study and thus couldn't give exact burden of disease in whole state of Punjab, which is a major limitation of the study. Also, short follow-up and partly retrospective nature of the study was another limitation in the study.

CONCLUSION(S)

Thus, the study concludes that IgAN is a common entity seen in this part of India. IF is the diagnostic modality used for IgAN. Hence, it should be done routinely on all the renal biopsies so as to reach an exact diagnosis. Also, renal biopsies practices followed by IF indications should be relaxed in this part of the world taking into consideration the high prevalence of IgAN here and IgAN frequently culminating into ESRD, if not diagnosed on time.

REFERENCES

[1] Berger J, Hinglais N. Intercapillary deposits of IgA-IgG. J Urol Nephrol. 1968;74(9):694-95.
[2] Walsh M, Sar A, Lee D, Yilmaz S, Benediktsson H, Manns B et al. Histopathologic features aid in predicting risk for progression of IgA nephropathy. Clin J Am Soc Nephrol. 2010;5(3):425-30.
[3] Shen PC, He LQ, Tang Y, Wang Q, Wang W, Li J. Clinicopathological characteristics and prognostic factors of asymptomatic IgA nephropathy. J Investig Med. 2010;58(3):560-65.
[4] Schena FP, Nistor I. Epidemiology of IgA Nephropathy: A global perspective. Semin Nephrol. 2018;38(5):435-42.
[5] Chandrika BK. IgA nephropathy in Kerala, India: A retrospective study. Indian J Pathol Microbiol. 2009;52(1):14-16.
[6] Sehgal S, Datta BN, Sakhuja V, Chugh KS. Primary IgA nephropathy: A preliminary report. Indian J Pathol Microbiol. 1995;38(3):233-37.
[7] Chowdry AM, Najar MS, Mir MM, Azad H, Rashid RA, Ashraf BM, et al. Primary IgA nephropathy in the Kashmiri population. Saudi J Kidney Dis Transpl. 2018;29(3):680-88.
[8] Magistroni R, D'Agati VD, Appel GB, Kiryluk K. New developments in the genetics, pathogenesis, and therapy of IgA nephropathy. Kidney Int. 2015;88(5):974-89.
[9] Haas M. IgA nephropathy and Henoch-Schoenlein purpura nephritis. In: Jennette JC, Oslen JL, Schwartz MM, Silva FG, editors Heptinstall's pathology of the kidney. 6th ed. Philadelphia: Lippincott Williams & Wilkins; 2007. Pp. 423-486.
[10] Berthoux F, Suzuki H, Thibaudin L, Yanagawa H, Maillard N, Mariat C, et al. Autoantibodies targeting galactose-deficient IgA1 associate with progression of IgA nephropathy. J Am Soc Nephrol. 2012;23(9):1579-87.
[11] Yeo SC, Cheung CK, Barratt J. New insights into the pathogenesis of IgA nephropathy. Pediatr Nephrol. 2018;33(5):763-77.
[12] Wyatt RJ, Julian BA. IgA nephropathy. N Engl J Med. 2013;368(25):2402-14.
[13] Barratt J, Feehally J. IgA nephropathy. J Am Soc Nephrol. 2005;16(7):2088-97.
[14] Mittal N, Joshi K, Rane S, Nada R, Sakhuja V. Primary IgA nephropathy in north India: is it different? Postgrad Med J. 2012;88 (1035):15-20.
[15] Rodrigues JC, Haas M, Reich HN. IgA Nephropathy. Clin J Am Soc Nephrol. 2017;12(4):677-86.
[16] Donadio JV, Grande JP. IgA nephropathy. New Engl J Med. 2002;347(10):738-48.
[17] Haas M. Histologic subclassification of IgA nephropathy: A clinicopathologic study of 244 cases. Am J Kidney Dis. 1997;29(6):829-42.
[18] Perse M, Veceric-Haler Z. The role of IgA in the pathogenesis of IgA nephropathy. Int J Mol Sci. 2019;20(24):6199.
[19] Cattran DC, Coppo R, Cook HT, Feehally J, Roberts ISD, Troyanov S, et al. The Oxford classification of IgA nephropathy: Rationale, clinicopathological correlations, and classification. Kidney Int. 2009;76(5):534-45.
[20] Culling CFA, Allison RT, Barr WT. Cellular Pathology Technique. 4th ed. London: Butterworth & Co; 1985:349-65.
[21] Maixnerova D, Reily C, Bian Q, Neprasova M, Novak J, Tesar V. Markers for the progression of IgA nephropathy. J Nephrol. 2016;29(4):535-41.
[22] Vanikar AV, Kanodia KV, Patel RD, Trivedi HL. Primary immunoglobulin A (IgA) nephropathy in Western India. Indian J Nephrol. 2005;15(4):227-31.
[23] Muzaffar S, Azad NS, Kayani N, Pervaz S, Ahmed A, Hasan SH. The frequency of IgA nephropathy at a single center in Pakistan. J Pak Med Assoc. 2003;53(7):301-05.
[24] Johnston PA, Brown JS, Braumholtz DA, Davison AM. Clinico-pathological correlations and long-term follow-up of 253 United Kingdom patients with IgA nephropathy. Q J Med. 1992;84(1):619-27.
[25] Tipu HN, Ahmed TA, Bashir MM. Clinical, histopathological and immunofluorescent findings of IgA nephropathy. Iran J Immunol. 2011;8(2):104-10.
[26] Chacko B, John GT, Neelakantan N, Balakrishnan N, Meshach G, Jacob CK. A ten year analysis on the renal outcomes and a model for estimating risk of progression. Indian J Nephrol. 2004;14:163-71.
[27] Siddappa S, Kowsalya R, Mythri KM. IgA nephropathy in a tertiary care center from south India. Indian L Nephrol. 2011;21(4):230-34.
[28] Simon P, Ramee MP, Autuly V, Laruelle E, Charasse C, Cam G, et al. Epidemiology of primary glomerular diseases in a French region. Variations according to period and age. Kidney Int. 1994;46(4):1192-98.
[29] Koyama A, Igarashi M, Kobayashi M. Natural history and risk factors for immunoglobulin A nephropathy in Japan. Am J Kidney Dis. 1997;29(4):526-32.
[30] Wang YT, Zhou CY, Zhu TC, Yang J, Zhang Y, Xu QY, et al. Analysis of kidney biopsy data from a single center in the midland rural area of China, 1996-2010. Curr Ther Res Clin Exp. 2013;74:22-25.
[31] Li PK, Ho KK, Szeto CC, Yu L, Lai FM. Prognostic indicators of IgA nephropathy in the Chinese – clinical and pathological perspectives. Nephrol Dial Transplant. 2002;17(1):64-69.
[32] Prakash S, Kanjanabuch T, Austin PC, Croxford R, Hsu CY, Choi AI, et al. Continental variations in IgA nephropathy among Asians. Clin Nephrol. 2008(5);70:377-84.
[33] Haas M, Rahman MH, Cohn RA, Shaykh SF, Ansari A, Bartosh SM. IgA nephropathy in children and adults: Comparison of histologic features and clinical outcomes. Nephrol Dial Transplant. 2008;23(8):2537-45.
[34] Trimarchi H, Muryan A, Young A, Forrester M, Iotti A, Pereyra H, et al. Dual renin-angiotensin system blockade plus oral methylprednisone for the treatment of proteinuria in IgA nephropathy. Medicina. 2007;67(5):445-50.

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