Validation of Oxford Classification of Immunoglobulin A Nephropathy

An Iranian Experience

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Introduction. In 2009, the Oxford classification of immunoglobulin A (IgA) nephropathy was proposed by the working group of the International IgA Nephropathy Network and Renal Pathology Society. It established specific pathologic features that predict the risk of progression of disease. This study aimed to evaluate the interobserver reproducibility of the Oxford classification of IgA nephropathy between Iranian nephropathologists.

Materials and Methods. We included 100 patients with primary IgA nephropathy diagnosed between 2001 and 2011. Histologic slides were circulated among 4 pathologists. A score sheet was answered by each individual pathologist for each biopsy, according to the instruction of the Oxford classification. Reproducibility was determined for each variable, using intraclass correlation coefficient (ICC).

Results. The ICC values calculated for each major category of the Oxford classification were as follows: the highest score of 0.94 for tubular atrophy and interstitial fibrosis; 0.8 for glomerular basement membrane duplication, extracapillary proliferation, and segmental endocapillary proliferation; and 0.1 to 0.3 for arterial lesions, especially for hyalinosis of arterioles and intimal thickening of arcuate vessels and interlobar arteries.

Conclusions. The Oxford classification of IgA nephropathy is a useful tool and evidenced-based method with high interobserver reproducibility in pathology reporting. Our data suggest that Oxford classification may be used as a model for classification of other renal pathologies in the future.

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INTRODUCTION

Immunoglobulin A (IgA) nephropathy is among the most common primary forms of glomerulonephritis. Patients have different clinical courses and progression to end-stage renal disease takes place in 20% of the cases in 10 consecutive years.[1] As such, it is crucial to diagnose the disease in its early stages of progression when the therapeutic intervention is still effective.[2-5]

Histologically, IgA nephropathy is diagnosed by deposition of IgA-dominant or IgA-codominant immune complexes within glomeruli, shown by immunofluorescence or immunohistochemistry.[6-8] In 2009, the working group of the International IgA Nephropathy Network and the Renal Pathology Society introduced for the first time

the Oxford classification of IgA nephropathy, which identifies 4 histologic features with independent values in predicting the renal outcome: the mesangial hypercellularity score (M), segmental glomerulosclerosis (S), endocapillary hypercellularity (E), and tubular atrophy/interstitial fibrosis (T) which are forming the MEST score.[9-12] The MEST score in the Oxford classification was defined after a provisional analysis of 40 cases by which variables of high interobserver reproducibility were chosen and other histologic features that may be found in IgA nephropathy with clinical significance were also assessed.

Recently, several validation studies of the Oxford classification have been published.[13-15] Given the clinical importance of the Oxford classification of IgA nephropathy, validation of this classification in Iran was deemed necessary for evaluating patient's condition and predicting the prognosis. This study intended to evaluate the interobserver reproducibility of the Oxford classification of IgA nephropathy between Iranian nephropathologists.

MATERIALS AND METHODS

We conducted a cross-sectional study on 100 kidney needle biopsies referred to our tertiary hospital between 2001 and 2011. All samples were diagnosed as biopsy-proven IgA nephropathy with confirmation of immunofluorescence and electron microscopy examination. The inclusion criteria used in this study were identical with the inclusion criteria used in the Oxford study. Patients with comorbid conditions such as diabetic nephropathy, lupus nephritis, and Henoch-Schoenlein purpura were excluded. Needle biopsies with less than 8 glomeruli were also excluded.[15-18]

Demographic data of patients were collected. Histologic slides, with a maximum number of glomeruli, which stained with periodic acid-Schiff and Jones methods, were marked and circulated among 4 pathologists. A score sheet was filled out by each pathologist for each biopsy specimen, according to the instructions of the Oxford classification. For a better understanding and correlation between pathologists, coordination meetings had been held before initiation of the study.

In evaluating MEST score, mesangial hypercellularity (M) was subclassified as follows: mild, moderate, and severe. Endocapillary hypercelllarity (E) was defined as an increase in the number of cells in glomerular capillary lumina, narrowing the lumen. Segmental sclerosis (S) was defined as any amount of tuft involved by obliteration of capillary lumen by increasing extracellular matrix with or without hyalinosis and adhesion. Tubular atrophy/interstitial fibrosis (T) was defined by thick irregular tubular basement membranes with a decrease in the diameter of tubules and scored according to the percentage of cortical area involvement, whichever was greater.[14-16] In addition to the MEST score, other histologic findings were assessed, the same as the initial Oxford study,[14] such as extracapillary proliferation (fibro and cellular crescent), arteriolar hyalonosis, and glomerular basemembranes (GBM).

Duplication of GBM was defined as a double contour of the GBM with or without endocapillary hypercellularity. Extracapillary lesions were subclassified as cellular, fibrocellular, and fibrous crescents. Arterial lesions were scored based on the most severe lesions. Interlobar and arcuate vessels were scored separately. Intimal thickness and arteriolar hyalinosis was considered as the portion of affected arterioles (zero, 1% to 25%, 25% to 50%, and > 50%).

After collecting data, reproducibility was determined for each variable, using the intraclass correlation coefficient (ICC). The ICC is a measure of reproducibility applicable to multiple raters. By convention, 0.4 to 0.59 is moderate interobserver reliability, 0.6 to 0.8 is good, and more than 0.8 is considered an outstanding score.[15-17] For qualitative variables, the chi-square test was used and a *P* value less than .05 was considered as significant. The analyses were carried out using the SPSS software (Statistical Package for the Social Sciences, version 16.0, SPSS Inc, Chicago, Ill, USA).

RESULTS

Biopsy samples of 100 patients were selected for the study after considering the exclusion criteria (71 men and 29 women). The patients' mean age was 36.5 ± 12.0 years. The ICC values calculated for each major category of the MEST between the four pathologists were as follows: the highest score of 0.94 for tubular atrophy and interstitial fibrosis, while it was 0.8 for GBM duplication, extracapillary proliferation, and segmental endocapillary proliferation.

Table 1. Intraclass Coefficient Class of Quantitative Scores Between 4 Pathologists

Variable	Intraclass Coefficient Class	*P*
Scorable glomeruli	0.970	< .001
Mesangial score	0.747	< .001
Global sclerosis	0.953	< .001
Tubular atrophy	0.949	< .001
Intrestitial fibrosis	0.949	< .001
Intrestitial inflammation	0.898	< .001
Segmental sclerosis+adhesion	0.899	< .001
Endocapillary hypercellularity (segmental and global)	0.755	< .001
Endocapillary hypercellularity (glomerular basement membrane duplication)	0.801	< .001
Total extracapillary lesion-cellular	0.906	< .001
Total extracapillary lesion-cellular (powered)	0.941	< .001
Total extracapillary lesion-fibrocellular	0.811	< .001
Total extracapillary lesion-fibrocellular (powered)	0.840	< .001
Total extracapillary lesion cellular and fibrocellular	0.857	< .001
Total extracapillary lesion cellular and fibrocellular (powered)	0.920	< .001

Extracapillary lesions were divided into cellular, fibrocellular, and fibrous categories, each group subclassified into 4 groups of (< 10%, 10% to 25%, 26% to 50%, and > 50%). The ICC was calculated for each group once and then all of them. For the arterial lesions, especially for hyalinosis of the arterioles, the ICC for intimal thickening of the arcuate vessels and interlobar arteries was 0.1 to 0.3, which meant the interobserver reproducibility in this field was very low (Table 1). Arteriolar hyalinosis was also classified into 3 subgroups (10% to 25%, 26% to 50%, and > 50% of arterioles involved), whereas none of them had an acceptable ICC (0.24 to 0.30). Even arteriosclerosis and intimal thickening showed significant differences between the raters (ICC varied between 0.3 and 0.5).

The biopsy cases were also divided into 2 categories of those with mesangial hypercellularity and those with normal mesangial cellularity; however, the calculated ICC showed no significant difference in any variables.

DISCUSSION

Immunoglobulin A nephropathy is among the most common causes of primary glomerulonephritis.[1-3] Although it is like a benign process, it could progress slowly into end-stage renal disease. Several investigations have been performed to find out the predictive factors of disease progression. While variable histologic features in light microscopy has been introduced for classification of the IgA nephropathy, there is no consensus on a general approach.[7,8]

Cattran and colleagues[15] proposed the new Oxford classification of IgA nephropathy in 2009, which focused on pathologic variables that could affect patients' prognosis. However, this classification needs to be validated in different cohorts of patients. To the best of our knowledge, 3 studies were published in Japan, China and Sweden on validation of the Oxford classification for pediatric IgA nephropathy,[17,18] and several studies about adult IgA nephropathy have been designed, which mostly focused on the prognostic importance of the MEST score in clinical settings.

In addition to the original Oxford study, Herzenberg and colleagues[16] conducted a cohort study on 187 adults and children with IgA nephropathy from 4 centers in North America for validation of the Oxford classification, by comparing the predictive value of each of the four lesions. Each pathological variable showed the same predictive value in both cohorts, except mesangial hypercellularity, which was weaker than the original study. Coppo and associates[17] examined 1147 patients from 13 European countries that encompassed the whole spectrum of IgA and demonstrated that the MEST score independently could predict the loss of estimated glomerular filtration rate. Kfoury and colleagues[19] studied on 70 patients and demonstrated that endocapillary hypercellularity and tubular atrophy were significantly associated with reduced initial estimated glomerular filtration rate and higher proteinuria.

In comparison with other recent studies, in

Table 2. Comparison of Intraclass Coefficient Class of Quantitative Variables Between Different Studies

Variable	Cattran et al[14]	Roberts et al[15]	Current Study
Mesangial hypercellularity score	0.64	0.37	0.57
Total glomeruli with segmental sclerosis	0.46	0.94	0.95
Total glomeruli with adhesion	0.20	0.76	0.91
Total glomeruli with endocapillary proliferation	0.57	0.87	0.75
Cortex with tubular atrophy	0.79	0.98	0.94
Cortex with interstial inflammation	0.78	0.98	0.94

our study, the interobserver reproducibility between pathologists with regards to quantitative variables was higher and in most occasions was more than 90%. The highest ICC belonged to the total number of scorable glomeruli. Agreement between pathologists in segmental sclerosis, tubular atrophy and interstitial fibrosis was more than 90%, resembling the latter abovementioned studies.[16,17,20-22] For segmental endocapillary proliferations, the ICC was poor. On the contrary, for global endocapillary hypercellularity, the ICC was good. Therefore, it is logical to consider the total endocapillary hypercellularity for better reproducibility.

In comparison with other studies, GBM duplication, segmental sclerosis, and adhesion have shown better reproducibility in this study, and it seems combination of slides stained with Jones and periodic acid-Schiff methods could help for better diagnosis.

In evaluating MEST score and 2 additional parameters, arterial hyalinosis and extracapillary proliferation (crescent), the ICC of endocapillary proliferation was 0.7, whereas in the Oxford study and Roberts and colleagues' study,[14,15] it was 0.57 and 0.87, respectively. Segmental sclerosis' ICC was 0.95, whereas in these studies, it was 0.94 and 0.46, respectively. Tubular atrophy and interstitial fibrosis' ICC was 0.94, whereas in the Oxford study and Roberts and colleagues' study, it was 0.79 and 0.98, respectively. For arteriolar hyalinosis, the ICC was 0.3, whereas in these studies, it was 0.6 and 0.7, respectively (Table 2). In summary, approximately all ICCs were higher for each of the pathologic variables in comparison with the initial Oxford study and closer to Roberts and colleagues' results, except for arterial hyalinosis and intimal thickening.

With regards to extracapillary lesions (crescent), the agreement on powered studies was higher, and the same result was also achieved in our study. However, the use of this calculation in routine working is not yet approved. Reviewing the literature, the importance of E (endocapillary proliferation) and C (crescent) in patient prognosis is controversial. With regards to pediatric categories, although less studied, T (tubular atrophy and interstitial fibrosis) seems to have the highest impact on prognosis.[18] Therefore, it seems that more prospective international studies are needed to be conducted in different settings. Meta-analysis studies for each item of the Oxford classification and its impact on patient's prognosis is then required to achieve a consensus statement for IgA nephropathy diagnosis.

CONCLUSION

The Oxford classification of IgA nephropathy is a useful evidenced-based method with high interobserver reproducibility between nephropathologist and seems suitable for achieving a consensus pathology report in this setting. Our data suggest that the Oxford classification may be used as a model for classification of other renal pathologies in the future.

CONFLICT OF INTEREST

None declared.

REFERENCES

1. Glassock RJ. IgA nephropathy: challenges and opportunities. Cleve Clin J Med. 2008;75:569-76.
2. Walsh M, Sar A, Lee D, et al. Histopathologic features aid in predicting risk for progression of IgA nephropathy. Clin J Am Soc Nephrol. 2010;5:425-30.
3. Wyatt RJ, Julian BA, Baehler RW, et al. Epidemiology of IgA nephropathy in central and eastern Kentucky for the period 1975 through 1994. Central Kentucky Region of the Southeastern United States IgA Nephropathy DATABANK Project. J Am Soc Nephrol. 1998;9:853-8.
4. Gharavi AG, Yan Y, Scolari F, et al. IgA nephropathy, the most common cause of glomerulonephritis, is linked to 6q22-23. Nat Genet. 2010;26:354-7.

5. 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;58:560-5.
6. Donadio JV Jr, Grande JP. Immunoglobulin A nephropathy: a clinical perspective. J Am Soc Nephrol. 1997;8:1324-32.
7. Falk RJ, Jennette JC, Nachman PH. IgA nephropathy. In: Brenner BM, editor. Brenner & Rector's the kidney. 6th ed. WB Saunders; 2000. p. 1302-10.
8. Ibels LS, Gyory AZ, Caterson RJ, et al. Primary IgA nephropathy:natural history and factors of importance in the progression of renal Impairment. Kidney Int Suppl. 2007;61:S67-70.
9. Radford MG Jr, Donadio JV Jr, Bergstralh EJ, Grande JP. Predicting renal outcome in IgA nephropathy. J Am Soc Nephrol. 200;8:199-207.
10. Reich HN, Troyanov S, Scholey JW, Cattran DC; Toronto Glomerulonephritis Registry. Remission of proteinuria improves prognosis in IgA nephropathy. J Am Soc Nephrol. 2007;18:3177-83.
11. Walsh M, Sar A, Lee D, et al. Histopathologic features aid in predicting risk for progression of IgA nephropathy. Clin J Am Soc Nephrol. 2010;5:425-30.
12. van Es LA. Pathogenesis of IgA nephropathy. Kidney Int. 1992;41:1720-9.
13. Walsh M, Sar A, Lee D, et al. IgA nephropathy. J Am Soc Nephrol. 2005;16:2088-97.
14. Roberts IS, Cook HT, Troyanov S, et al. The Oxford classification of IgA nephropathy: pathologydefinitions, correlations, and reproducibility. Kidney Int. 2009;76:546-56.
15. Cattran DC, Coppo R, Cook HT, et al. The Oxford classification of IgA nephropathy: rationale,clinicopathological correlations, and classification. Kidney Int. 2009;76:534-45.
16. Herzenberg AM, Fogo AB, Reich HN, et al. Validation of the Oxford classification of IgA nephropathy. Kidney Int. 2011;80:310-7.
17. Coppo R, Troyanov S, Bellur S, et al. Validation of the Oxford classification of IgA nephropathy in cohorts with different presentations and treatments. Kidney Int. 2014;86:828-36.
18. Le W, Zeng CH, Liu Z, et al. Validation of the oxford classification of IgA nephropathy for pediatric patients from china. BMC Nephrol 2012;13:158.
19. Kfoury H, Alsuwiad A, Hussain S, et al. External validation of oxford classification of IgA nephropathy: A retrospective study of 70 patents from Saudi Arabia. HK Nephropathol. 2014;16:29-33.
20. Choi BS. Validation Study of the Oxford Classification for IgA Nephropathy in Korean Adults. Korean J Intern Med. 2012;27:275-7.
21. Lv J, Shi S, Xu D, et al. Evaluation of the Oxford Classification of IgA Nephropathy: A Systematic Review and Meta-analysis. Am J Kidney Dis. 2013;62:891-9.
22. Tesar V, Troyanov S, Bellor S, et al. Corticosteroids in IgA nephropathy: A retrospective analysis from the VALIGA study. J Am Soc Nephrol. 2015;26:2248-58.

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