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Persistent microhaematuria with negative or low proteinuria

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"Take nothing on its looks; take everything on evidence. There's no better rule." (Charles Dickens)

ABSTRACT

The level of proteinuria continues to be the clinical parameter that is best related to the development of long-term renal failure in glomerular pathologies. This quantity is particularly important when we analyse the progression of patients with IgA nephropathy. As such, the natural progression of patients with IgA who clinically present with normal kidney function, microhaematuria and low proteinuria had not been analysed comprehensively until the Spanish multicentre study herein analysed. After studying 141 Caucasian patients with biopsied IgA nephropathy and a "benign" clinical profile and after they were classified histologically in accordance with the new Oxford classification, it could be concluded that the renal prognosis of these patients was excellent. This is the first study in the literature that demonstrates the usefulness of this new classification in patients who clinically have normal renal function and proteinuria below 0.5g/day. The latest advances in the genetics of this disease, as well as in the collaboration of complement pathways in its pathophysiology mean that these results cannot be extrapolated to all the populations studied. In addition, the analysis and follow-up of microhaematuria has regained importance as an independent prognostic factor for developing renal failure, although there are no consistent studies in this regard yet. However, it is a subject that should be examined again by the nephrology community.

Keywords: Microhaematuria. Proteinuria. IgA nephropathy. Oxford classification.

Microhematuria persistente con proteinuria negativa o de escasa cuantía

RESUMEN

La cuantía de la proteinuria continúa siendo el parámetro clínico que mejor se relaciona con el desarrollo de insuficiencia renal a largo plazo en las patologías glomerulares. Esta cuantía es especialmente importante cuando se analiza la evolución de los pacientes afectos de una nefropatía IgA. De esta manera, la evolución natural de los pacientes con nefropatía IgA que se presentan clínicamente con función renal normal, microhematuria y proteinuria escasa no había sido analizada con profundidad hasta la elaboración de este trabajo multicéntrico español que aquí se analiza. Tras estudiar a 141 pacientes caucásicos con nefropatía IgA biopsiada y presentación clínica «benigna» y clasificarlos histológicamente de acuerdo a la nueva clasificación de Oxford, se puede concluir que el pronóstico renal de estos enfermos es excelente. Este es el primer trabajo de la literatura en el que se demuestra la utilidad de esta nueva clasificación en los pacientes que clínicamente se presentan con función renal normal y proteinuria inferior a 0,5 g/día. Los nuevos avances en la genética de esta enfermedad, así como en la colaboración de las vías del complemento en su fisiopatogenia misma, hacen que estos resultados no sean extrapolables a todas las poblaciones estudiadas. Por otro lado, el análisis y seguimiento de la microhematuria ha recobrado importancia como factor pronóstico independiente para el desarrollo de insuficiencia renal, aunque aún no existen estudios consistentes al respecto. Sin embargo, es un tema que debe ser nuevamente considerado por la comunidad nefrológica.

Palabras clave: *Microhematuria. Proteinuria. Nefropatía IgA. Clasificación de Oxford.*

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Different studies have analysed the clinical and biochemical parameters related to the risk of long-term progression in

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patients with IgA nephropathy (IgAN). Classically, proteinuria greater than 1g/day, the presence or development of high blood pressure (HBP) and a low glomerular filtration rate on diagnosis have been prognostic factors significantly related to the development of chronic kidney disease (CKD).[1-3] However, and unlike other glomerular processes, in IgAN patients, proteinuria between 0.5 and 1g/day is also associated with a risk of developing CKD.[4-6] Many studies on IgAN prognosis do not include patients who only have microhaematuria and low proteinuria (0.5-1g/day) at diagnosis. This represents a high percentage of patients, particularly in countries with "very active" renal biopsy policies. From a histological point of view, the two strongest predictors of progression of the nephropathy have been tubulointerstitial damage and the presence of glomerulosclerosis. Hence, it can be inferred that most prognostic factors used to predict the risk of long-term kidney function loss refer to chronic and advanced lesions. Therefore, we can justify the need to carry out studies to identify prognostic variables from data obtained at diagnosis or before advanced renal fibrosis lesions appear in renal biopsies.

The recent Oxford classification, validated for the North American and Asian adult and child populations and pending definitive validation for the European population (VALIGA study), highlights that histological lesions of mesangial proliferation (M1), endocapillary proliferation (E1), focal segmental hyalinosis (S1) and tubulointerstitial involvement (T1-2) are independent predictors of progression beyond clinical parameters (including proteinuria and glomerular filtration rate).[7,8] However, this classification was not validated in a population that displayed normal kidney function and low proteinuria (proteinuria ≤0.5g/day) clinically.

The study recently published under the title "Long-term outcome of IgA nephropathy presenting with minimal or no proteinuria" presented the results of 141 Caucasian patients diagnosed histologically with IgAN with normal kidney function, proteinuria equal to or lower than 0.5g/day and persistent microhaematuria.[9] This was a study by GLOSEN (Spanish Society of Nephrology Glomerular Disease Study Group) that retrospectively included patients from eight Spanish hospitals that had an "active" renal biopsy policy over an extended period (1975-2008). 64% of patients studied were males, with a mean age of 23.7, followed up over a median period of 108 months, and no patient had renal failure on diagnosis. After this extended follow-up period, only 5 (3.5%) patients suffered a 50% increase in their baseline creatinine level, and only 1 (0.7%) patient had a 100% increase and no patient developed end-stage renal disease. At the end of the study, only 21 (14.9%) patients had proteinuria higher than 0.5g/day and only 6 (4.2%) of the 21 had proteinuria higher than 1g/day, which is a significant risk factor for developing end-stage renal disease.[1] Furthermore, the increase in HBP in the population studied was very small (from 16.3% to 21.3%). This study contributed information on the percentage of patients who achieved "spontaneous" clinical remission and we consider this clinical information to be very important. Although spontaneous clinical remission had previously been well-described, it had not been studied specifically.[10] In this study, 53 patients (37.5%) achieved spontaneous clinical remission, defined by the disappearance of microhaematuria, proteinuria of less than or equal to 0.2g/day and normal kidney function and blood pressure.

From a histological point of view, this was the first study published in which the Oxford classification was applied to patients with IgAN and proteinuria of less than 0.5g/day and the data obtained is interesting. The first thing that it showed, as was expected, is that endocapillary proliferation and focal segmental hyalinosis lesions were uncommon (8.5% and 15.6% respectively), and that 95% did not have significant tubulointerstitial involvement. However, mesangial proliferation lesions appeared in 46 (32.6%) patients in the study. These results are of great importance, since despite the low number of events, the multivariate study showed that focal segmental hyalinosis lesions were the only independent factor significantly associated with renal survival (increase >50% baseline serum creatinine, primary objective). In addition, an absence of mesangial proliferation greater than 50% was significantly and independently associated with the possibility of achieving spontaneous remission in the multivariate study. Furthermore, patients with hyalinosis lesions had higher baseline proteinuria figures with a significantly more marked increase during follow-up with respect to those who did not have them. The only patient whose baseline serum creatinine figures doubled during the follow-up period had M1E1S1T1 lesions. All these data confirm the usefulness of the Oxford classification in patients who present with a "benign" profile.

As has been described in randomised, controlled clinical trials, proteinuria level has an important influence on long-term kidney progression, even in these types of patients who have a favourable presentation and progression.[1-6,11,12] In this study, in confirmation of previous assertions, we were able to demonstrate that the only clinical variable that influenced long-term renal survival was mean proteinuria during follow-up (time-average [TA]-proteinuria). TA-proteinuria was the only independent clinical risk factor that predicted an increase in baseline creatinine by more than 50% and at the same time baseline proteinuria was significantly related with the probability of achieving remission. These results highlight the crucial role of proteinuria level on the long-term progression of this disease. In addition, we should mention that this favourable progression was achieved without the need for immunosuppressant treatment. In patients who had proteinuria higher than 0.5g/day or HBP, angiotensin

converting enzyme (ACE) inhibitors or angiotensin II receptor blockers (ARBs) were used. At the end of the follow-up period, 55 (41.8%) patients were receiving ACE inhibitors/ARBs.

Before this study, only Asian studies described the prognosis of patients with IgAN and low proteinuria. These studies, unlike the study mentioned in this article, highlight that renal prognosis was not so favourable in these patients.[13-15] Indeed, in the study by Szeto et al. that analysed 72 Chinese patients with normal kidney function, normal blood pressure and proteinuria lower than 0.4g/day, 33% developed proteinuria higher than 1g/day, 26% developed HBP and kidney function deteriorated in 7%.[14] These results were also confirmed in a more recent study, carried out on 177 Chinese patients with normal blood pressure and proteinuria lower than 0.4g/day, in which 24% developed renal failure and only 9% achieved clinical remission.[15] In addition to the potential pathological differences that there may be in the different studies, it is likely that the differences in genetic susceptibility of the Asian population explain prognostic differences. There are many and an increasing number of observations that suggest a significant genetic contribution to the pathogenesis of IgAN, based on family and demographic studies. These observations began with differences in prevalence of the nephropathy in the different ethnic groups and there continue to be major genome-wide association studies that identify the DQ loci of the HLA histocompatibility system involved consistently in the susceptibility to develop IgAN in patient groups of European and Asian descent, as has been demonstrated in recent studies by Feehally et al. and Yu et al.[16,17]. Familiar linkage studies have provided the strongest evidence for genetic factors involved in the development and progression of IgAN. These studies also demonstrate their strong influence on hyperglycosylated IgA composition in serum.[18] Different genetic loci have been identified in familial forms of IgAN and they have been related to the nephropathy's pathogenesis (6q22-q23, 2q36, 4q26-q31, 17q12-q22), although a specific gene has not yet been identified.[19] Even so, one of the most important studies is that published by Gharavi et al., which demonstrated, after studying European and Asian populations, mutations in complement regulatory factor H (CFH) 1 and 3 of chromosome 1q32, only in the Asian population with IgAN, findings that bring to the table the potential involvement of the alternative complement pathway in the pathogenesis of this disease.[20]

The information contributed by the study on 141 Caucasian patients is important for establishing the progression profile of IgAN and selecting the clinical and/or histological findings that may predict poor progression. Given the good current policy of not performing biopsies on this patient group, it is very unlikely that a study of these characteristics can be repeated. However, given that these patients can develop proteinuria, HBP and renal failure, a lifetime annual follow-up is recommended to monitor these parameters and start treatment with ACE inhibitors/ARBs in those who develop the abovementioned abnormalities. However, we must bear in mind that in this patient group, it is essential to perform a broad differential diagnosis that includes benign familial haematuria (thin basement membrane disease), as well as more common causes of microhaematuria with low proteinuria, without forgetting all urological diseases that should be ruled out beforehand. Perhaps the most important decision is to explain what microhaematuria should be assessed and followed-up clinically, given its high frequency in normal clinical practice, and even more so following the study published by Vivante et al. in *JAMA*, which has revolutionised the potential prognostic role of microhaematuria.[21] Haematuria is a common finding in diseases that cause glomerular damage and its estimated frequency varies between 0.18% and 16.1%, depending on the population studied. Isolated microhaematuria, when not accompanied by HBP, significant proteinuria or kidney function abnormalities, has traditionally been related to a good prognosis.[22] However, the information contained in the study by Vivante et al. of a population of one million Israeli soldiers who presented with isolated microhaematuria following screening studies, has partially changed the image that people had about this clinical finding. In this young population (16-25 years of age), microhaematuria prevalence was 0.4% in males and 0.2% in females after almost 22 years of follow-up, which was associated with an adjusted hazard ratio of 18.5 for developing end-stage renal disease. However, and without detracting from the importance of the study, it has a lack of follow-up over time and a lack of essential clinical data such as proteinuria and HBP development. Although the study on which this article is based sheds light on the potential long-term progression of patients with IgAN and few renal manifestations, it has not been able to answer the question "what is the prognosis of patients with microhaematuria?" or determine whether microhaematuria is an independent risk factor for developing end-stage renal disease. Although we suspect that the disappearance of microhaematuria may be related to a "benign" progression of IgAN, studies whose primary objective is this assumption are required. In the Spanish multicentre study, we attempted to relate the disappearance of microhaematuria to better renal progression, but perhaps the lack of renal events made it impossible to establish this association.

Classical studies related macroscopic haematuria outbreaks with good renal prognosis in IgAN patients, but recent studies have denied this assertion after demonstrating that there is at least a 25% risk of developing CKD following these outbreaks,[23,24] and as such, we require more studies that analyse the factors potentially involved in the physiopathology of micro- and macrohaematuria, which could help us understand the disease and its progression better.[25-28] As nephrologists, a lot of our focus has been on proteinuria and perhaps haematuria has been neglected. However, this factor should receive more attention nowadays.

KEY CONCEPTS

1. As a practical message, the results of this study reinforce the current view prevailing amongst the nephrological community that a renal biopsy should not be performed in patients with clinical manifestations similar to those of the study: persistent microhaematuria with proteinuria that is negative or lower than 0.5g/day.
2. The most likely diagnosis in these patients is IgAN or benign familial haematuria, but the definitive determination of both diagnoses by renal biopsy (which requires immunofluorescence and electron microscope) does not seem necessary, due to the excellent progression of the vast majority of cases.
3. It is necessary to carry out a comprehensive differential diagnosis for microhaematuria at the start of follow-up.
4. The regular monitoring of these patients is recommended (check-ups every year or every three years, depending on individual characteristics), due to the possibility of a gradual increase in proteinuria over the years.

In summary, we consider that this study contributes important information to characterising the natural history and prognosis of IgAN, and has demonstrated the usefulness of the Oxford classification in this patient group for the first time.

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Conflicts of interest

The authors declare that they have no conflicts of interest related to the contents of this article.

REFERENCES

1. 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.
2. Bartosik LP, Lajoie G, Sugar L, Cattran DC. Predicting progression in IgA nephropathy. Am J Kidney Dis 2001;38:728-35.
3. Alamartine E, Sabatier JC, Guerin C, Berliet JM, Berthoux F. Prognostic factors in mesangial IgA nephropathy. An extensive study with univariate and multivariate analysis. Am J Kidney Dis 1991;18:12-9.
4. Barbour SJ, Reich HN. Risk stratification of patients with IgA nephropathy. Am J Kidney Dis 2012;59:865-73.
5. Berthoux F, Mohey H, Laurent B, Mariat C, Afiani A, Thibaudin L. Predicting the risk for dialysis or death in IgA nephropathy. J Am Soc Nephrol 2011;22:752-61.
6. Coppo R, D´Amico G. Factors predicting progression of IgA nephropathies. J Nephrol 2005;18:503-12.
7. Working Group of the International IgA Nephropathy Network and the Renal Pathology Society, Cattran DC, Coppo R, Cook HT, Feehally J, Roberts IS, Troyanov S, et al. The Oxford Classification of IgA nephropathy: rationale, clinicopathological correlations, and classification. Kidney Int 2009;76:534-45.
8. Working Group of the International IgA Nephropathy Network and the Renal Pathology Society, Coppo R, Troyanov S, Camilla R, Hogg RJ, Cattran DC, Cook HT, et al. The Oxford IgA nephropahty clinicopathological classification is valid for children as well as adults. Kidney Int 2010;77:921-7.
9. Gutiérrez E, Zamora I, Ballarín JA, Arce Y, Jiménez S, Quereda C, et al.; Grupo de Estudio de Enfermedades Glomerulares de la Sociedad Española de Nefrología (GLOSEN). Long-term outcome of IgA nephropathy presenting with minimal or no proteinuria. J Am Soc Nephrol 2012;23:1753-60.
10. Costa RS, Droz D, Noel LH. Long-standing spontaneous clinical remission and glomerular improvement in primary IgA nephropathy (Berger´s Disease). Am J Nephrol 1987;7:440-6.
11. Praga M, Gutiérrez E, González E, Morales E, Hernández E. Treatment of IgA nephropathy with ACE inhibitors: A randomized and controlled trial. J Am Soc Nephrol 2003;14:1578-83.
12. Coppo R, Peruzzi L, Amore A, Piccoli A, Cochat P, Stone R, et al. IgACE: A placebo-controlled, randomized trial of angiotensin-converting enzyme inhibitors in children and young people with IgA nephropathy and moderate proteinuria. J Am Soc Nephrol 2007;18:1880-8.
13. Lai FM, Szeto CC, Choi PC, Li PK, Chan AW, Tang NL, et al. Characterizacion of early IgA nephropathy. Am J Kidney Dis 2000;36:703-8.
14. Szeto CC, Lai FM, To KF, Wong T, Chow KM, Choi PC, et al. The natural history of immunoglobulin A nephropathy among patients with hematuria and minimal proteinuria. Am J Med 2001;110:434-7.

15. Shen P, He L, Huang D. Clinical course and prognostic factors of clinical early IgA nephropathy. Neth J Med 2008;66:231-3.
16. Feehally J, Farrall M, Boland A, Gale DP, Gut I, Heath S, et al. HLA has strongest association with IgA nephropahty in genome-wide analyses. J Am Soc Nephrol 2010;21:1791-7.
17. Yu XQ, Li M, Zhang H, Low HQ, Wei X, Wang JQ, et al. A genome-wide association study in Han Chinese identifies multiple susceptibility loci for IgA nephropathy. Nat Genet 2011;44:178-82.
18. Barratt J, Feehally J. Primary IgA nephropathy: new insights into pathogenesis. Semin Nephrol 2011;31:349-60.
19. Glassock RJ. The pathogenesis of IgA nephropathy. Curr Opin Nephrol Hypertens 2011;20:153-60.
20. Gharavi AG, Kyriluk K, Choi M, Li Y, Hou P, Xie J, et al. Genome-wide association study identifies susceptibility loci for IgA nephropathy. Nature Genetics 2011;43:321-7.
21. Vivante A, Afek A, Frenkel-Nir Y, Tzur D, Farfel A, Golan E, et al. Persistent asymptomatic isolated microscopic hematuria in Israeli adolescents and young adults and risk for end-stage renal disease. JAMA 2011;306:729-36.
22. Gale D. How benign is haematuria? Using genetics to predict prognosis. Pediatr Nephrol 2013;28:1183-93.
23. Gutiérrez E, González E, Hernández E, Morales E, Martínez MA, Usera G, et al. Factors that determinate an incomplete recovery of renal function in macrohematuria-induced acute renal failure of IgA nephropathy. Clin J Am Soc Nephrol 2007;2:51-7.
24. Gutiérrez E, Egido J, Rubio-Navarro, Buendía I, Blanco-Colio LM, Toldos O, et al. Oxidative stress, macrophage infiltration and CD163 expression are determinants of long-term renal outcome in macrohematuria-induced acute kidney injury of IgA nephropathy. Nephron Clin Pract 2012;121:c42-53.
25. Moreno JA, Martín-Cleary C, Gutiérrez E, Toldos O, Blanco-Colio LM, Praga M, et al. AKI associated with macroscopic glomerular hematuria: clinical and pathophysiologic consequences. Clin J Am Soc Nephrol 2012;7:175-84.
26. Moreno JA, Martín-Cleary C, Gutiérrez E, Rubio-Navarro A, Ortiz A, Praga M, et al. Haematuria: the forgotten CKD factor? Nephrol Dial Transplant 2012;27:28-34.
27. Eitner F, Floege J. In search of a better understanding of IgA nephropathy-associated hematuria. Kidney Int 2012;82:513-5.
28. Floege J. The pathogenesis of IgA nephropathy: what is new and how does it change therapeutic approaches? Am J Kidney Dis 2011;58:992-1004.

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