Kidney Res Clin Pract 31 (2012) 203–204

Kidney Research and Clinical Practice

journal homepage: http://www.krcp-ksn.com
Contents lists available at ScienceDirect

Editorial

Cytokine gene polymorphisms: Can these differentiate renal disease entities?

Immunoglobulin A (IgA) nephropathy (IgAN) is one of the most common causes of primary glomerulonephritis (GN), and shows diverse clinical presentations, leading to progressive renal failure in some patients [1]. The etiology of IgAN is considered to be multifactorial [2]. The genetic factors may influence disease susceptibility and the likelihood of the disease progressing to end-stage renal disease. Evidence for a genetic contribution has come from the observation that some families are affected in an apparently autosomal dominant fashion, although this is not common [3–5]. Furthermore, ethnicity seems to influence susceptibility to the disease and impacts upon disease progression. The prevalence of IgAN varies among racial groups, as is most common among Asians and American Indians, intermediate in Hispanics and Caucasians, and rare in African and American blacks. In addition to the genetic determinants of disease susceptibility, there are genetic associations with the tendency for IgAN to progress. The analyses of the genetic polymorphisms of several cytokines and chemokines have been widely performed for the elucidation of genetic determinants of IgAN regarding susceptibility and progression.

Thin basement membrane nephropathy (TBMN) is one of the most common causes of persistent hematuria in children and adults, the other main etiologies being Alport's syndrome and IgAN [6,7]. Besides hematuria, patients with TBMN usually have minimal proteinuria, normal renal function, and uniformly thinned glomerular basement membranes (GBMs), as determined by electron microscopy [8]. In some patients, microscopic hematuria is intermittent and may not be detected until adulthood. Episodic gross hematuria, often in association with upper respiratory tract infections, which is typical for IgAN, is not unusual. TBMN was originally known to have a benign clinical course associated with family history. Overt proteinuria and hypertension are unusual in TBMN. Other glomerular disorders, such as IgAN and focal or global glomerulosclerosis, may occur concurrently with TBMN, altering the usual natural clinical course and histopathology of the condition [6]. Voskarides et al. reported that in cases of combined focal segmental glomerulosclerosis on biopsy, the prognosis was not good in a significant proportion of patients [9]. TBMN mainly manifests as an inherited disorder with autosomal dominant transmission affecting approximately one-half of successive generations. Approximately two-thirds of patients with TBMN have at least one other relative with hematuria. The remaining one-third of patients may have *de novo* mutations or the nonpenetrance in other members of the family. About half of TBMN is caused by the mutation of *COL4A3*/*COL4A4* genes of type IV collagen, and the remainders occur sporadically [7].

IgAN is diagnosed by the predominant deposition of IgA in the mesangial region, therefore it cannot be made without a renal biopsy, no matter how suggestive the clinical presentation may be. Serum IgA is often increased, and there may be IgA in cutaneous blood vessels. Serum complement concentrations are normal. These findings, however, are not reliable enough to support the diagnosis without a renal biopsy. Mesangial IgA occurs in other conditions, such as lupus nephritis, alcoholic liver disease, and IgA monoclonal gammopathy, which can usually be differentiated on clinical, serologic, and histologic criteria. None of the light microscopic features are of themselves diagnostic of IgAN.

The diagnosis of TBMN is also confirmed by a renal biopsy and genetic analyses [8]. The GBM does not reveal any structural abnormalities, but it is characteristically thinned, sometimes having only approximately half of the thickness expected in a normal kidney. Endothelial cells and podocyte foot processes maintain normal morphological features. The characteristic manifestation of TBMN is persistent hematuria of glomerular origin; therefore, it is important to distinguish this benign disease from other, superimposing causes of glomerular hematuria, such as IgAN, postinfectious GN, mesangiocapillary GN, and lupus nephritis. Whereas IgAN and TBMN may be difficult to distinguish on clinical grounds alone, other forms of GN are frequently associated with additional clinical features that rarely are seen in TBMN, such as proteinuria, hypertension, renal impairment, and systemic symptoms. Genetic analysis is useful for discrimination between Alport syndrome and TBMN. Segregation of the disease with the *COL4A5* locus and sequencing of all of the exon regions can reveal over 80% of the mutations in X-linked Alport syndrome. Sequencing of the *COL4A3* and *COL4A4* genes is also required for the diagnosis of familial forms of TBMN [7].

In this issue of *Kidney Research and Clinical Practice*, Jung et al. report the results of their investigation into the effects of gene polymorphisms on the development of IgAN and TBMN of several cytokines including interleukin-18 (IL-18), transforming growth factor-β (TGF-β), and vascular endothelial growth factor (VEGF) in Korean patients [10]. Furthermore, they tried to discriminate

http://dx.doi.org/10.1016/j.krcp.2012.10.001

between IgAN and TBMN by using the differences between these cytokine gene polymorphisms without a renal biopsy. In the study, the frequencies of the IL-18-607CC genotype and the VEGF 405GG genotype were significantly increased in IgAN patients compared with the control group, whereas no significant differences in genotype frequency were observed between TBMN and control groups. There were no significant differences, however, in genotype and allele frequencies between IgAN and TBMN groups. The authors concluded that their study did not show any statistically significant differences in the six selected gene polymorphisms of IL-18, TGF-β, and VEGF between IgAN and TBMN, and additional extensive studies are required to clarify the potential role of gene polymorphism in discriminating between IgAN and TBMN without a renal biopsy.

Cytokines are polypeptide regulatory hormones that are produced during the activation and effector phases of innate and specific immunity, and constitute a cellular signaling system. They serve to mediate and regulate immune and inflammatory responses, and have many functional roles in GN [11]. Chemokines cover a large family of structurally homologous cytokines that share an ability to stimulate leukocyte motility and directed movement, and act as inflammatory mediators. In the kidney, several chemokines are present in the glomeruli or tubulointersitium, and they are considered to have active roles in renal damage. Considering the characteristics of cytokines and chemokines, such as pleiotropism, redundancy, production by multiple diverse cell types, and influences on the action of other molecules, an evaluation of integrated working networks of cytokines and chemokines is required for the elucidation of their roles in the pathogenetic mechanisms of glomerulonephritides. Until now, lots of studies dealt with these subjects by studying different cytokines, however, genetic diversity including gene polymorphisms of various cytokines has not been determined as a definite initiator or modulator of primary GN.

The differentiation between IgAN and TBMN is quite important because of their different clinical courses and approaches to treatment [1,12]. Contrary to the benign nature of TBMN, a substantial proportion of IgAN patients progresses to end-stage renal disease. As I mentioned above, we should consider the complexity and diversity of cytokines and chemokines in the understanding of their roles in the development or progression of primary GN. Ideally we should figure out the integrated working system of cytokines. Unfortunately, the networks of cytokines and chemokines are still evolving. We cannot therefore consider the genetic analyses of several cytokines as a definite diagnostic tool for the differentiation of renal diseases at present.

The pathogenetic mechanisms of IgAN and TBMN are quite different. Whereas TBMN is considered a genetic disorder involving GBM type IV collagen, the pathogenesis of IgAN is still hypothetical and associated with multiple factors, including immunological abnormalities producing abnormal IgA. Considering all the aspects of pathogenetic mechanisms, the theoretical concepts of the authors, that is, that differential diagnosis of IgAN and TBMN can be achieved with the genetic analyses of limited number of cytokines, seems to be impractical [10]. The classical diagnostic methods including a renal biopsy are definitely needed to discriminate between these two common diseases causing persistent hematuria.

Conflict of interest

None to declare.

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Available online 16 October 2012

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