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Ethnicity and IgA nephropathy: worldwide differences in epidemiology, timing of diagnosis, clinical manifestations, management and prognosis

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ABSTRACT

Immunoglobulin A nephropathy (IgAN), the most common primary glomerulonephritis, is one of the major causes of end-stage renal disease. Significant variances in epidemiology, clinical manifestation, timing of diagnosis, management and renal prognosis of IgAN have been reported worldwide. The incidence of IgAN is the most frequent in Asia, followed by Europe, and lower in Africa. Moreover, Asian patients show more frequent acute lesions in renal histology and present poorer renal outcomes compared with Caucasians. The comorbidities also show the difference between Asians and Caucasians. Although the frequency of gross hematuria with upper respiratory tract infection is not different, comorbidities with gastrointestinal diseases are reported to be higher in Europe. Recently, genetic studies for variant ethnic patients revealed widely ranging genetic risks in each ethnicity. A genetic risk score is most elevated in Asians, intermediate in Europeans and lowest in Africans, consistent with the disease prevalence of IgAN globally. Ethnic variance might be highly affected by the difference in genetic background. However, it is also essential to mention that the different timing of diagnosis due to variant urinary screening systems and the indication for renal biopsy in different countries may also contribute to these variances. The management of IgAN also varies internationally. Currently, several novel therapies based on the pathogenesis of IgAN are being assessed and are expected to become available soon. Further understanding the ethnic variance of IgAN might help establish individualized care for this disease. Here, we review the issues of ethnic heterogeneities of IgAN.

Keywords: corticosteroid, ethnicity, genetics, IgA nephropathy, tonsillectomy

INTRODUCTION

Immunoglobulin nephropathy (IgAN) is the most common primary glomerulonephritis worldwide, characterized by the deposition of IgA in the glomerular mesangial region. Pathological diagnosis using renal biopsy is essential to make a definitive diagnosis. Around 40% of patients progress to end-stage renal disease (ESRD) over 20 years [1]. Most cases are asymptomatic, but some cases present gross hematuria, often concurrent with upper respiratory tract or gastrointestinal infections. Therefore, abnormal mucosal immune responses to exogenous antigens are considered to be involved in its pathogenesis.

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Galactose-deficient IgA1 (Gd-IgA1), which lacks galactose in O-linked glycans of the hinge region of IgA1, is a key effector molecule in the pathogenesis of IgAN [2]. Autoantibodies against Gd-IgA1 form immune complexes with Gd-IgA1, which deposit in the mesangial regions and induce glomerular inflammation. These serial processes are advocated as Gd-IgA1 multi-hit pathogenesis of IgAN [3].

Regarding the prevalence of IgAN, there are regional and racial differences. Familial IgAN is also observed, especially in Western countries [4, 5]. Recent genome-wide association studies (GWAS) have identified some genetic loci associated with the risk of developing and progression of IgAN. Moreover, genetic risk alleles for IgAN were found to be more frequent in Chinese than in Europeans, which correlates with the epidemiological patterns [6]. These facts tell us there is some genetic background in this disease. Furthermore, the screening systems and management strategies are also different in each region. Here, we reviewed the issues of ethnic or regional heterogeneities of IgAN.

EPIDEMIOLOGY

The incidence of adult IgAN is estimated at least 25 cases per million population yearly (pmp/year) worldwide, the highest among other glomerular diseases including membranous nephropathy (12 pmp/year), minimal change disease (8 pmp/year), focal segmental glomerulosclerosis (6 pmp/year) and membranoproliferative glomerulonephritis (2 pmp/year) [7]. The prevalence of IgAN varies largely depending on the geographic distribution. IgAN is most frequent in Asia, followed by Europe, and least in Africa [8], for example, 39–45 cases pmp/year in Japan [9], 25–31 cases pmp/year in France [10] and 9.9 cases pmp/year in the UK [11]. The frequency of IgAN in primary glomerular disease also varies worldwide [8, 12]. IgAN accounts for more than 40% in some countries, such as Japan [13], China [14], France [10] and Germany [15]. On the other hand, it accounts for less than 10% of Bangladesh [16], India [17], Latin America [12] and African countries [18]. These differences may be partly due to the various indications for renal biopsy in each country, but diversity in the genetic background also plays a significant role.

The abovementioned data could be underestimated since most IgAN is asymptomatic and renal biopsy is essential for a definitive diagnosis. Furthermore, the degree of underestimation is likely to vary from country to country, as urinary screening systems and indications for renal biopsy differ internationally. While systematic mass screening of urine in populations is widespread in some Asian countries such as Japan [19], Korea [20], Taiwan [21] and Singapore [22], it is not common in Western countries [23].

The male-to-female ratio of IgAN also shows regional differences. A Japanese cohort enrolling 871 patients and a Chinese cohort enrolling 988 patients showed that the ratio of males to females was 1:1.4 [24, 25]. On the other hand, the cohort data from Europe or the USA showed that the ratio of males to females was around 2:1 [26, 27]. While the regional differences in IgAN might be partly due to environmental factors, differences in disease-susceptibility genes among races are also identified, explaining racial diversity in this disease. In fact, geographic variation in the genetic risk for IgAN worldwide was indicated to be the highest for East Asians and Native Americans, intermediate for Middle Easterners and Europeans, and the lowest median scores for Africans [28].

PATHOGENESIS

Gross hematuria induced by respiratory tract infections in patients with IgAN and the association of IgAN with bowel diseases has been considered evidence of a mucosa–kidney axis in IgAN [29]. Although the exact mechanism of synthesizing Gd-IgA1 is not clear enough, several researchers suggest that mucosal immune dysregulation might be involved in producing Gd-IgA1 [30, 31]. The disease-susceptibility genes of IgAN, which GWAS identified, are associated with mucosal barrier and response to mucosal pathogens [32]. Nephritogenic IgA production due to abnormal mucosal immune response might be involved in the mucosa–kidney axis in IgAN.

Whether nasopharyngeal-associated lymphoid tissues (NALT) or gastrointestinal tract-associated lymphoid tissues (GALT) is the main responsible site of abnormal immune response in IgAN has been discussed [33]. To date, several studies have demonstrated the efficacy of tonsillectomy in treating IgAN, especially in Asian countries [34–39]. The favorable effect of tonsillectomy in lowering the risk of renal outcomes supports the involvement of NALT in the pathogenesis of IgAN, at least in Asian patients. In Europe, many reports of IgAN combined with gastrointestinal complications such as celiac disease, Crohn's disease, ulcerative colitis and irritable bowel syndrome have been reported [40–42]. Based on a clinical survey on the clinical presentation of patients with IgAN in Europe and Japan, the number of IgAN with gastrointestinal complications is reported to be 17% in Europe, while it is 1% in Japan [42]. Previously, the gut–kidney crosstalk in IgAN has been much discussed in Europe [30, 43]. Recently therapeutic strategies targeting GALT, such as targeted-release formulation of budesonide (TRF-budesonide), have been developed [44, 45].

However, according to a clinical survey, the incidence of gross hematuria coincident with upper respiratory tract infection is not significantly different between Japan (29.8%) and Europe (22.7%) [42]. These facts indicate that abnormal immune responses of NALT might be involved in both Asian and European patients. Indeed, a retrospective cohort study including 264 Caucasian patients also indicated the efficacy of tonsillectomy in delaying the progression of IgAN, mainly in patients with gross hematuria [46]. Further prospective investigations of the effectiveness of tonsillectomy in Caucasian patients are required. The degree of responsibility of each mucosal immune tissue may differ in each ethnicity and affect the clinical symptoms and even treatment response.

GENETIC CHARACTERISTICS

Genetic factors affect the pathogenesis of IgAN. Several GWAS performed in different ethnicities have identified the risk genetic loci associated with the development of IgAN. Some of the identified genes are associated with mucosal immunity (*ITGAM*, *ITGAX*, *DEFA*, *LIF*, *OSM*, *HORMAD2*, *MTMR3* and *TNFSF13*), both innate and adaptive immunity (*CARD9*, *VAV3*, *HLA-DQA1*, *HLA-DQB1* and *HLA-DRB1*), and complement activation (*CFH*, *CFHR1* and *CFHR3*) [32, 47].

A genetic risk score based on the GWAS-identified loci is highest in Asians, intermediate in Europeans and lowest in Africans, consistent with the variation in disease prevalence among Asian, European and African populations [28, 48]. The study comparing the genetic risk score of diverse ethnicities in the USA still showed a similar tendency: US Asian-Americans showed the highest genetic risk, US white Americans intermediate and US African-Americans the lowest [49]. Racial

differences in disease-susceptibility genes were also examined using Chinese and European cohorts. In this study, Li et al. showed that mucosal immunity- and complement-related genes were more strongly associated with Chinese than with Europeans [50]. These findings suggest that genetic factors are involved in racial and regional differences in the development of IgAN.

GWAS for serum Gd-IgA1 levels, using Asian and European populations, discovered two genome-wide significant loci, in *C1GALT1* and *C1GALT1C1* [51]. These genes encode enzymes essential for the *O*-glycosylation of IgA1. Notably, the frequency of these risk alleles is also reported to be different between Asians and Europeans, which also indicates the racial variety of IgAN.

TIMING OF DIAGNOSIS

IgAN is usually asymptomatic; its initial manifestation is often hematuria, which generally appears earlier than proteinuria. Therefore, urine screening is an effective way to detect the early stage of IgAN. In Japan, annual urinalysis targeting children began in 1974 as a national system for early detection of kidney disease [19]. Due to the widespread screening system, most cases of IgAN in Japan are detected by abnormal urinary findings such as microscopic hematuria and proteinuria. A study investigating the prevalence of urine abnormalities in annual urinary screening at school reported the prevalence of urinary abnormalities was 0.52% among elementary school children and 0.75% among junior high school children in Japan [52]. Furthermore, it has been reported that the proportion of ESRD due to glomerulonephritis has significantly decreased in the generation after the initiation of urinary screening compared with that before the initiation of screening [53]. Early detection and referral to nephrologists due to the urinalysis screening program may help reduce the number of ESRD due to glomerulonephritis.

Based on the above successful experience, dipstick urine tests have been included in the Japanese nationwide mass screening program, Specific Health Checkup, which started in 2008 and targets all adults between 40 and 74 years of age [54]. Moreover, the cost-effectiveness of mass screening for dipstick urine tests has been analyzed and the results suggested that it could be justifiable as an efficient use of finite healthcare resources [55, 56]. A retrospective cohort study for a large-scale Japanese health checkup including 2104 persons showed that 3-year repetitive isolated hematuria is associated with glomerulonephritis [57]. In addition, a longitudinal analysis of annual health check-up at university health service, including 13 640 young participants, suggested the effectiveness of multi-year annual urinalysis in identifying the high-risk group for glomerulonephritis [58]. These results indicate the usefulness of applying mass urinary screening programs worldwide. Indeed, nationwide mass urinary screening for school children has been conducted in Taiwan since 1990 [59] and Korea since 1998 [20]. A study of 630 students aged 6–15 years with positive urinary screening in Taiwan reported that glomerular nephritis is the major cause of urinary abnormalities [60]. A study surveying Korean school urinalysis screening from 1998 to 2004 showed isolated proteinuria was about 0.2%, and occult blood was about 0.8%. Furthermore, IgAN was noted in 43.8% of renal biopsy cases due to urinary abnormalities [20]. However, nationwide systematic mass urinary screening is currently limited in several Asian countries and is not common in Western countries. The difference in the screening system may affect the clinical stage of IgAN at the time of renal biopsy in each country.

Renal biopsy is essential for the diagnosis of IgAN. Histopathological findings are important for prognostic prediction and determining therapeutic strategies in IgAN. However, there is no consensus on the indication for renal biopsy, especially in patients who present microscopic hematuria with subtle proteinuria (<0.5 g/day). This situation can arise in the early phase of IgAN. Such cases might be detected by systematic mass screening of urine in populations conducted in some Asian countries. Therefore, IgAN might be diagnosed in an earlier phase in these Asian countries than in European countries. Indeed, a clinical survey comparing the Japanese and European cohorts reported that the frequency of preserved estimated glomerular filtration rate (eGFR) (>60 mL/min/1.73 m^2) at the time of renal biopsy was low in Europe (55%) compared with Japan (71%) [42]. These data also support that IgAN was possibly diagnosed in an earlier phase in Asian countries with the systematic mass screening of urine in populations.

Recently, novel biomarkers, including serum Gd-IgA1, serum glycan-specific antibodies and urinary Gd-IgA1, have been reported as potentially helpful in diagnosing IgAN [61–63]. Moreover, our research group recently reported anti–βII-spectrin IgA might also be involved in the pathogenesis of IgAN and could be the candidate for its disease-specific biomarker [64]. The screening system using novel biomarkers in addition to conventional screening can potentially reduce medical expenses [65]. Establishing an effective screening system may help to improve the renal prognosis of patients with IgAN and is further useful in reducing overall medical costs.

RENAL HISTOLOGY

The Oxford classification of IgAN is widely used to evaluate histological severity associated with renal prognosis, independent of clinical parameters [66]. Validation studies have been conducted worldwide and found that histopathological findings also showed regional differences. Active lesions such as endocapillary hypercellularity (E lesion) and crescent formation (C lesion) are more frequently observed in Asian cohorts than in Europe. E lesion was present in 42% of cases in the Japanese cohort, compared with 10%–14% in the European cohort, and C lesion was present in 48% of cases in Chinese and 63% in the Japanese cohort, compared with only 17% in the European cohort [67–70]. No differences in glomerulosclerosis or tubulointerstitial lesions were observed among the above cohorts. The variations in the characteristics of renal histopathology among the ethnicities indicate that the disease severities at the time of biopsy differ between races.

MANAGEMENT

Currently, there is no established disease-specific treatment for IgAN. Furthermore, the management strategies for IgAN vary internationally. In the KDIGO (Kidney Disease: Improving Global Outcomes) guideline, renin–angiotensin system (RAS) inhibitors, blood pressure control, cardiovascular risk management and lifestyle modification are listed as highly recommended management of IgAN [71]. Other treatment options, such as corticosteroids, nonsteroidal immunosuppressive agents and tonsillectomy (combined with steroid pulse therapy), remain controversial and are listed as second-line treatments only for selected cases in the KDIGO guideline. The evidence supporting the value of nonsteroidal immunosuppressive agents and tonsillectomy is inconsistent, especially when considered by ethnicity.

RAS inhibitors are widely used in both Japan and Europe, but corticosteroids are more frequent in Japan than in Europe [42, 72, 73]. Two large randomized controlled trials (RCTs) investigated the efficacy of corticosteroids in treating IgAN but suggested increased risks of adverse events with corticosteroids [74, 75]. The Supportive versus immunosuppressive Therapy for the treatment of Progressive IgA Nephropathy (STOP-IgAN) trial included 337 patients from Germany, and methylprednisolone was administered intravenously at a dose of 1 g/day for 3 days at the start of Months 1, 3 and 5, and oral prednisolone at a dose of 0.5 mg/kg per 48 h on the other days [74]. The Therapeutic Evaluation of Steroids in IgA Nephropathy Global (TESTING) trial involved 503 participants from Australia, Canada, China, India and Malaysia. In this trial, oral methylprednisolone was administered at 0.6–0.8 mg/kg/day and weaned off over 6–8 months [75]. However, the corticosteroid doses used in the above trials seem higher than in Japan [76, 77]. Furthermore, the two RCTs mentioned above have an important bias: the patients enrolled in these trials received treatment after a different time interval from the kidney biopsy. In the TESTING trial, due to an excess report of severe infection, the protocol was modified in 2016. The methylprednisolone dose was reduced to 0.4 mg/kg/day for 2 months, followed by weaning by 4 mg/day/month over 6–9 months. Furthermore, prophylaxis against *Pneumocystis jirovecii* pneumonia was given during the first 12 weeks of treatment [78]. With the low-dose corticosteroid, the steroid-treated group showed significantly reduced risks of kidney function decline, kidney failure or death due to kidney disease [79]. Thus, administering appropriate doses of steroids in selected patients and managing adverse effects might be recommended in IgAN patients.

One of the recent issues was the approval for clinical use of the TRF-budesonide (NEFECON®) as the first disease-specific treatment of IgAN by the US Food and Drug Administration in 2021. TRF-budesonide is a corticosteroid designed to be released at the terminal ileum, with the highest concentration in mucosal Peyer's patches. It undergoes rapid metabolization in the liver, and less than 10% of the drug enters systemic circulation [80]. In the Targeted-release Budesonide Versus Placebo in Patients with IgA Nephropathy (NEFIGAN) trial conducted in European countries, TRF-budesonide added to optimized RAS inhibitors significantly reduced proteinuria in patients with IgAN [44]. Moreover, the incidence of adverse events was similar between the TRF-budesonide group and the controls. Currently, the NefIgArd phase III trial evaluating TRF-budesonide is conducted across Europe, North America, South America and Asia Pacific. The interim analysis showed the patients with TRF-budesonide presented proteinuria reduction and eGFR preservation compared with the placebo [45]. Patients remain in follow-up in this trial, and confirmatory data are awaited to assess whether TRF-budesonide is effective in different ethnicities.

Regarding nonsteroidal immunosuppressive agents, the effectiveness of mycophenolate mofetil (MMF) and hydroxychloroquine (HCQ) has been reported in China. An RCT demonstrated the potential of MMF as a corticosteroid-sparing agent among patients from China [81]. On the other hand, a RCT including patients from the USA and Canada showed no benefit of MMF in reducing proteinuria in IgAN [82]. According to these results, the KIDGO guidelines suggest MMF should only be considered in Chinese patients [71]. A phase II clinical trial for HCQ in Chinese patients showed the effectiveness of HCQ in addition to optimized RAS inhibitors for reducing proteinuria in patients with IgAN over 6 months without evidence of adverse events [83]. Currently, the evidence for MMF and HCQ is limited to Chinese patients. Regarding other ethnicities, further investigation might be required.

Tonsillectomy combined with steroid pulse therapy (TSP) has become increasingly common in some Asian countries, especially Japan. TSP was first reported by Hotta et al. in 2001 [77]. The effectiveness of tonsillectomy in improving renal outcomes in IgAN patients has been confirmed in a recent meta-analysis and a large cohort study [38, 39]. According to these reports, the KDIGO guideline mentioned that tonsillectomy could be considered in Japanese patients [71]. Indeed, the proportion of chronic glomerulonephritis cases accounted for more than 40% of the diseases causing ESRD before the 1990s in Japan; however, in recent years, it has decreased to 20%–30% [84]. The widespread mass urine screening systems contribute to the early diagnosis, and developing TSP is considered to improve renal prognosis in patients with IgAN. On the other hand, a European cohort (European Validation Study of The Oxford Classification of IgA Nephropathy: VALIGA), pairing 41 patients with tonsillectomy and 41 without tonsillectomy with similar risk of progression, showed no significant difference in the renal outcome [85]. However, as mentioned above, the timing of diagnosis might be different in Asian and European countries. Thus, the timing of intervention with tonsillectomy may also be different in the Asian cohort and European cohort, explaining the reason why the Asian and European cohorts showed different results regarding the efficacy of tonsillectomy, even though there is no difference in the incidence of gross hematuria with upper respiratory tract infection. An RCT with long-term follow-up might be required to verify the efficacy of tonsillectomy in European patients.

RENAL PROGNOSIS

In general, the disease progression of IgAN is relatively slow, but the clinical course of IgAN varies widely. Some patients have only asymptomatic microscopic hematuria or mild proteinuria, while some cases present rapid deterioration of renal function. Past studies indicated that Asian patients have a poorer prognosis than Caucasian patients [86]. In a follow-up study of 141 Caucasian patients with IgAN with asymptomatic hematuria and mild proteinuria (urinary protein <0.5 g/day), no patients developed ESRD, and 96.7% of patients maintained their serum creatinine levels at less than 50% increase at 10 years and 91.9% at 20 years [87]. Meanwhile, in a Japanese retrospective cohort with 871 patients, the renal survival rate was 87.5% at 10 years and 72.6% at 20 years, even with an average urinary protein level of 0.68 g/day and normal renal function at diagnosis [25]. These data suggest that IgAN in Asians may have a worse prognosis than Caucasians, even if the proteinuria at diagnosis showed the same degree [86]. However, other factors, such as the timing of intervention, treatment strategies and comorbidities, should be considered when interpreting prognostic factors.

Recently, Barbour et al. established a clinical prediction model based on a large multi-ethnic cohort study [88]. This model included age, blood pressure, proteinuria, eGFR at renal biopsy, the histologic score (MEST-C), using RAS inhibitors at renal biopsy, using corticosteroids at renal biopsy and racial characteristics. This model has been validated in several studies [89–91]; however, this clinical prediction model is intended for use at the point of diagnosis. Therefore, the limitation of this model may not reflect the effect of treatment after biopsy.

Moreover, the above-mentioned prediction model does not include the status of hematuria. Although the importance of proteinuria during the clinical course of IgAN has been well

discussed by several studies [92–94], recent cohort studies and a meta-analysis have also demonstrated the importance of hematuria [95–97]. A retrospective cohort study using medical data from 1 203 626 young armed forces employees aged 16 through 25 years in Israeli revealed that persistent asymptomatic isolated microscopic hematuria is a significant risk for ESRD especially for adolescents and young adults [98]. Furthermore, a recent analysis of a 10-year follow-up cohort study including 684 IgAN patients showed the clinicopathological manifestation of patients with persistent high-degree hematuria was more severe, and the prognosis was worse than for those with persistent low-degree hematuria [99]. Therefore, hematuria may be an indicator of early diagnosis of IgAN. At the same time, it reflects the disease activity of IgAN and would be one of the therapeutic indexes. Further large cohort observational study is needed to evaluate these findings.

CONCLUSIONS

Although the disease definition of IgAN is simple, the clinical manifestations are widely variable. Moreover, the screening system, diagnostic strategies and management also vary internationally. Nowadays, several disease-specific therapies for IgAN are being investigated and are expected to become available in the near future. Understanding the ethnic variance of IgAN is essential to establish individualized management.

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DATA AVAILABILITY STATEMENT

No new data were generated or analyzed in support of this research.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

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