The effects of angiotensin-converting enzyme gene polymorphism on the progression of immunoglobulin A nephropathy in Malaysian patients

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ABSTRACT

Introduction: Angiotensin-converting enzyme (ACE) gene polymorphism, especially the deletion/deletion (DD) genotype, is associated with the disease progression of immunoglobulin A (IgA) nephropathy patients in various studies from both Asia Pacific and European populations. However, recent studies within the same populations were unable to reproduce the same results. Hence, we had studied the distribution of the DD genotype, the association between ACE gene polymorphism and the disease progression, and the factors (other than ACE gene polymorphism) which were involved in the disease progression of our local patients.

Methods: This was a cross-sectional study of biopsy-proven IgA nephropathy patients attending the Nephrology Clinic, Hospital Universiti Kebangsaan Malaysia. Both biochemical and urine tests at the time of first presentation were compared to those at the time of the study, and the disease progression was analysed. The ACE gene polymorphism was identified via PCR-amplification technique, and patients were then categorised into the DD and the non-DD groups for detailed analysis. Histological severity of each renal biopsy was scored according to the predetermined criteria and medications used were recorded. The association between the gene polymorphism and disease progression was then determined. The patients who were stable or had renal function deterioration, were respectively regrouped into Groups 1 and 2, to identity those factors (other than ACE gene polymorphism), which were involved in the disease progression.

Results: 60 patients with adequate renal histopathological examination were recruited. Their mean age was 40.9 +/− 12.3 years and the follow-up duration was 4 +/− 3 years (range 6 months–20 years). More than two-thirds of them were treated with ACE inhibitors or angiotensin receptor blockers and 8.3 percent received the combination treatment. The DD genotype was noted in 13.3 percent of study patients, insertion/insertion in 48.3 percent and insertion/deletion genotype in 38.3 percent. Although the estimated glomerular filtration rate (eGFR) of both groups were the same during their initial presentation, the DD patients had more severe disease compared to the non-DD patients at the time of the study. Their serum creatinine and eGFR was 178 (IQR 31.3) μmol/L and 42.1 +/− 31.1 ml/min/1.73 square metres, whereas the non-DD patients had serum creatinine and eGFR of 79 (IQR: 88.3) μmol/L and 76.6 +/− 42.1 ml/min/1.73 square metres, respectively (p-value is less than 0.01). The DD patients were also found to have more severe vascular damage in their renal biopsies compared to the non-DD patients. The annual rate of decline in eGFR was not significantly different between the two groups. It was −5.7 +/− 2.2 ml/min/1.73 square metres/year for the DD group and −4.8 +/− 2.0 ml/min/1.73 square metres/year for the non-DD group (p-value is equal to 0.5). They also had severe proteinuria with UPCI of 0.09 (IQR 0.2) g/mmol creatinine vs. 0.04 (IQR 0.10) g/mmol creatinine (p-value is less than 0.01). The study also confirmed that patients who had higher systolic blood pressure, greater proteinuria and longer follow-up duration had significant renal function deterioration compared to those who did not.

Conclusion: The DD genotype, although found in a minority of the patients, might have adversely affected the disease progression of our IgA nephropathy patients. Higher systolic blood pressure, greater proteinuria and longer follow-up duration were the other prognostic factors in IgA nephropathy patients. However, appropriate treatment, especially prompt use of renin-angiotensin-aldosterone system blockade, should stabilise the disease regardless of their genotype.

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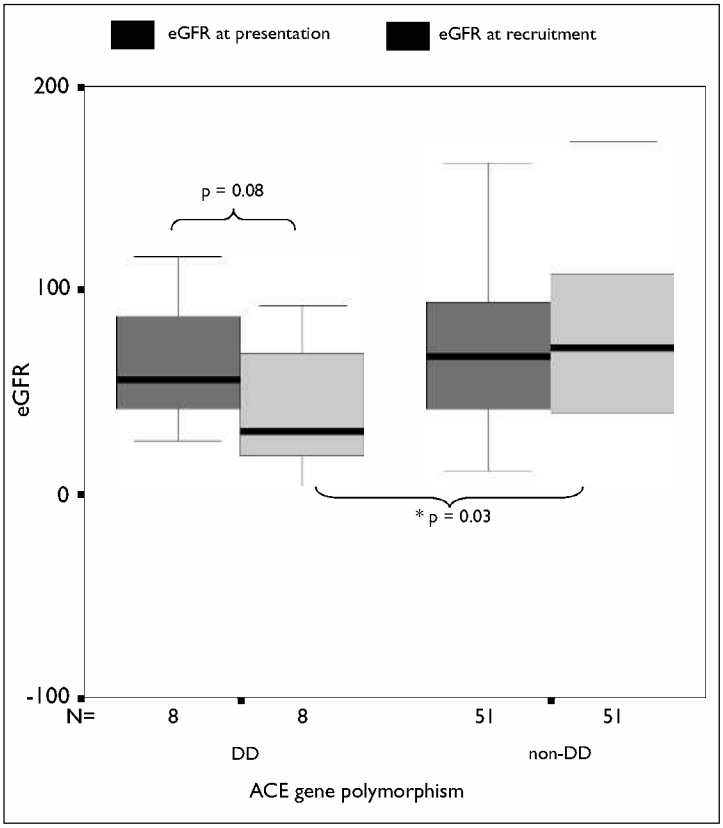
INTRODUCTION

Immunoglobulin A nephropathy (IgAN) is the commonest cause of primary glomerulonephritis worldwide. However, its frequency differs among the various regions.[1] Local figures suggested that it accounts for 40% of biopsy-proven, primary glomerulonephritis.[2] It is not a benign disease; in fact one-third of the patients progresses to end-stage renal disease after 10–15 years of follow-up and some present with severe azotaemia. Since its first description by Berger in 1967, the definite aetiology is still unknown, but the aberrant, polymeric immunoglobulin A molecule predisposes kidneys to inflammation and mesangial cells proliferation.[3] Both environmental and genetic factors have been found to be involved in the disease onset and progression. Angiotensin-converting enzyme (ACE) gene polymorphism, angiotensinogen as well as uteroglobin gene polymorphism have been widely studied, alone or in combination.[4-6]

The ACE gene is localised to the chromosome 17q23 and ACE is its main product. Both insertion (I) and deletion (D) polymorphism has been identified at intron 16, and the ACE gene genotypes, i.e. II, ID or DD, have been studied in IgAN patients previously. The DD genotype, which had a higher serum ACE level, can predispose the IgAN patients to a severe disease with poor prognosis compared to the non-DD genotype patients.[7,8] However, the association between the DD genotype and poor disease progression has been demonstrated only in a few of the studies.[9-12] Hence, we performed this study to determine the distribution of ACE gene genotypes, the association between the DD genotype and disease progression and other factors which determine the disease progression in our local IgAN patients.

METHODS

A cross-sectional study of 60 patients from Nephrology Clinic, Hospital Universiti Kebangsaan Malaysia (HUKM) was conducted in November 2005. The study was approved by the local research and ethical committee. The patients had been followed-up from 1986 to April 2005. All of them had biopsy-proven, primary IgAN. Both clinical examination and laboratory parameters were recorded; these include renal function test, liver function test, full blood count, lipid profile, random blood sugar, urine microscopy and early morning, spot urine protein-creatinine index (UPCI). The investigational chart at the time of the first presentation was reviewed and



	eGFR at presentation	eGFR at recruitment	p (intragroup)
DD	64.2	42.2	0.08
Non-DD	71.0	76.5	0.22
p (intergroup)	0.62	0.03*	

Fig. 1 Boxplot shows the ACE gene polymorphism and disease progression in the DD and non-DD patients.

the same parameters were compared. Their glomerular filtration rate (GFR) was estimated with Cockroft and Gault formula and the patients were classified into the chronic kidney disease (CKD) stage I-V according to the National Kidney Foundation's Kidney Disease Outcomes Quality Initiative (NKF/ KDOQI) classification. Disease progression was estimated from the changes in their serum creatinine, estimated GFR (eGFR) and UPCI.

3 ml of fresh venous blood (< 72 hours) was sampled into ethylenediaminetetraacetic acid bottles and through the polymerase chain reaction-amplification technique, the DNA sequence was processed in a biotechnology laboratory within a specified environment. It was then extracted and primer sequences of CTG GAG ACC ACT CCC ATC CTT TCT and GAT GTG GCC ATC TTC GTC AGA T were used to determine the ACE gene polymorphism. Both the D and I polymorphism at 190 bp and 490 bp, respectively, were identified with agarose gel electrophoresis and ethionamide bromide.[13] The patients were then grouped into the DD and non-DD groups; the latter comprised those with the II and ID genotypes for analysis. Both renal function and disease progression

Table I. Biochemical parameters of study patients at the time of presentation and at the time of the study.

Parameters	At presentation	At recruitment	p-value	Normal range
Haemoglobin (g/dL)	12.7 (IQR 1.8)	13.0 (IQR 3.3)	0.38	4.0–10.0
Sodium (mmol/L)	138 (IQR 4.8)	138.5 (IQR 2.6)	0.03	13–150
Potassium ± SD (mmol/L)	4.2 ± 0.6	4.4 ± 0.5	0.03	3.5–5.0
Urea (µmol/L)	5.4 (IQR 4.5)	5.0 (IQR 6.7)	0.05	2.5–6.4
Creatinine (µmol/L)	90 (IQR 68)	90.5 (IQR 98)	0.43	44–80
Uric acid (µmol/L)	426.1(IQR 144.8)	468.4 (IQR 121.0)	0.04 *	149–450
Protein (g/L)	71 (IQR 11.3)	75 (IQR 6.0)	< 0.01 *	67–88
Albumin (g/L)	41 (IQR 8.8)	42 (IQR 5.0)	0.03 *	35–50
Hb A1c (%)	5.6 (IQR 0.6)	5.7 (IQR 0.9)	0.66	< 6.5
Cholesterol (mmol/L)	6.3 (IQR 2.3)	5.2 (IQR 1.0)	< 0.01 *	< 5.7
Triglyceride (mmol/L)	1.4 (IQR 1.6)	1.3 (IQR 1.1)	0.16	< 1.4
HDL (mmol/L)	1.4 (IQR 0.8)	1.4 (IQR 0.8)	0.67	> 1.2
IgA ± SD (mg/L)	275 ± 101	411.9 ± 195.3	0.5	70–473
IgM ± SD (mg/L)	179.2 ± 97.9	144.8 ± 70.2	0.24	34–265
IgG (mg/L)	1,240 (IQR 625.9)	1,590 (IQR 562.5)	0.89	931–1,916
Urine RBC (Dipstix)	3 (IQR 2)	2 (IQR 2)	< 0.01 *	0–1
UPCI (g/mmol)	0.2 (IQR 0.3)	0.06 (IQR 0.1)	< 0.01 *	< 0.02
eGFR ± SD (ml/min/1.73m^2)	70.0 ± 35.7	72 ± 42.3	0.67	90–120

* p-value is statistically significant
SD: standard deviation; IQR: interquartile range

Table II. Clinical and laboratory parameters of the DD and the non-DD groups in the study population.

Parameters	DD	non-DD	p-value
Number	8	52	
Age at presentation ± SD (years)	36.5 ± 13	34.9 ± 11	0.71
Age at recruitment ± SD (years)	47.2 ± 14	40.0 ± 11.8	0.12
MAP ± SD (mmHg)	96.1 ± 9.9	93.8 ± 14.7	0.67
BMI ± SD (kg/m^2)	26.7 ± 6.0	25.7 ± 5.8	0.68
Creatinine at presentation (µmol/L)	111 (IQR 49.8)	89 (IQR 6,938)	0.21
Creatinine at recruitment (µmol/L)	178 (IQR 31.3)	79 (IQR 88.3)	0.007*
eGFR ± SD at presentation (ml/min/1.73m^2)	64.2 ± 30.4	70.9 ± 36.2	0.62
eGFR ± SD at recruitment (ml/min/1.73m^2)	42.1 ± 31.1	76.6 ± 42.1	0.03*
UPCI at presentation (g/mmol)	0.25 (IQR 0.2)	0.18 (IQR 0.28)	0.97
UPCI at recruitment (g/mmol)	0.09 (IQR 0.2)	0.04 (IQR 0.10)	0.04*
Albumin at presentation (g/L)	40 (IQR 8.8)	41.0 (IQR 9.0)	0.7
Albumin at recruitment (g/L)	40.3 (IQR 5.0)	42.0 (IQR 12.0)	0.54
Protein at presentation (g/L)	69.2 (IQR 7.2)	71.0 (IQR 12.0)	0.74
Protein at recruitment (g/L)	73.8 (IQR 6.8)	75.0 (IQR 6.0)	0.48
Cholesterol at presentation (mmol/L)	5.3 (IQR 6.6)	6.3 (IQR 2.3)	0.42
Cholesterol at recruitment (mmol/L)	6.2 (IQR 1.4)	5.01(IQR 0.8)	0.03*

* p-value is statistically significant

were compared between the two groups and changes in eGFR per year were determined.

Histological severity of renal biopsy was assessed according to the scoring system proposed by Claudio et al.[14] The glomerular, tubular, interstitial and vascular changes were scored independently with 0 for no changes, 1 for focal, 2 for multifocal and 3 for diffuse and severe changes. Patients were classified into mild, moderate and severe disease depending on their total score of 0–7, 8–14 and 15–21, respectively. The histological changes for each glomerular, tubular, interstitial and vascular lesion were also determined in relation to their genotype. According to their renal status, they were then regrouped into Groups 1 and 2 for analysis of other prognostic factors. Group 1 was those with stable renal function and Group 2 with renal function deterioration. Significant deterioration was defined as at least 50% worsening of eGFR or serum creatinine level.

Study data and statistical analysis were evaluated using the Statistical Package for Social Science version 11.5 (SPSS Inc, Chicago, IL, USA), and the values were presented as mean ± SD for parametric data and median ± IQR for non-parametric data. Chi-square (χ^2) test was used for categorical data, while Student's *t*-test was used for parametric, numerical data and Mann-Whitney U test was used for non-parametric data. The mean eGFR of the DD and non-DD groups was compared with the *t*-test, whereas changes in baseline biochemical data, with

Table III. Clinical and laboratory parameters of Group 1 and Group 2 patients.

Parameter	Group 1 (Stable)	Group 2 (Deteriorated)	p-value
Number (%)	49 (81.7)	11 (18.3)	
Age ± SD at presentation (years)	35.5 ± 10.8	33.7 ± 13.1	0.65
Age ± SD at recruitment (years)	40.6 ± 12.1	42.6 ± 13.2	0.61
SBP (mmHg)	129.0 (IQR 16.7)	144.2 (IQR 25.0)	0.02*
Duration (years)	3.8 (IQR 3.2)	5.5 (IQR 15.4)	0.04*
Creatinine at presentation	89.0 (IQR 70.5)	94.0 (IQR 58.0)	0.6
eGFR ± SD at presentation (ml/min/1.73m^2)	70.5 ± 35.5	68. 2 ± 38.3	0.85
Doubling in serum creatinine	0	6	< 0.001*
UPCI at presentation (g/mmol)	0.16 (IQR 0.23)	0.22 (IQR 0.1)	0.33
UPCI at recruitment (g/mmol)	0.05 (IQR 0.09)	0.16 (IQR 0.1)	0.03*
Albumin at presentation (g/L)	41.0 (IQR 8.8)	39 (IQR 6.3)	6.3
Albumin at recruitment (g/L)	42.0 (IQR4.0)	41.0 (IQR 4.4)	0.8
Cholesterol at presentation (mmol/L)	6.4 (IQR 2.5)	5.6 (IQR 1.1)	0.1
Cholesterol at recruitment (mmol/L)	5.1 (IQR 1.0)	5.6 (IQR1.1)	0.1
HDL at presentation (mmol/L)	1.4 (IQR 0.8)	1.4 (IQR 0.8)	0.7
HDL at recruitment (mmol/L)	1.5 (IQR 0.4)	1.4 (IQR 0.8)	0.7

* p-value is statistically significant

Kruska Wallis or Student's *t*-test where appropriate. A p-value < 0.05 was considered as significant.

RESULTS

A total of 134 patients were screened and 60 of them had agreed to participate in the study. Female patients outnumbered male patients with a 2:1 ratio. Chinese comprised 56.7%, followed by Malays (41.7%), and Indians (1.6%). The mean age was 40.9 ± 12.3 years, with a median follow-up duration of four years (IQR 3, range six months–20 years). Mean systolic, diastolic blood pressures and MAP were 131.9 ± 19.4 mmHg, 74.8 ± 12.9 mmHg and 94.1 ± 14.1 mmHg, respectively. Dyslipidaemia and hypertension were common among the study patients, being found in 55% and 53.5%, respectively, followed by diabetes mellitus type 2 in 10%. During their first presentation, the mean age was 35 ± 5 years. Most of them (76%) had a mild histological lesion and the commonest presentation was proteinuria of more than 1 g/day with or without microscopic haematuria. It was found in 65% of the patients, especially in the 20–39 year age group. 80% of the patients were treated with ACE inhibitors (ACEIs) or angiotensin receptor blockers (ARBs) for hypertension and/or proteinuria, and 8.3% for the combination. Corticosteroid was used in 28%, especially for those with severe nephrosis or active crescentic glomerulonephropathy. The commonest immunosuppressant was low-dose "minipulse" intravenous cyclophosphamide. It was used in 23.3% of the patients, followed by cyclosporine A (8.3%) and azathioprine (1.7%). Almost half of the patients received fish oil as adjunctive therapy, dipyridamole in 30%, followed by aspirin in 6.7%. Most of them received more than a single agent at one time depending on their clinical status.

There were no significant changes in the haemoglobin, sodium, potassium, urea and creatinine, as well as eGFR both at the presentation and recruitment times (Table I). The mean eGFR was 72 ± 42.3 ml/min/1.73m^2 during the recruitment, compared to 70 ± 35.7 ml/min/1.73m^2 at the initial presentation (p = 0.67). The median serum uric acid level increased from 426 (IQR 144.8) to 468.4 (IQR 121.0) μmol/L (p = 0.04). Both sera protein and albumin improved significantly. Serum albumin improved from 41 (IQR 8.8) to 42 (IQR 5.0) g/L (p = 0.03), with a significant reduction in UPCI from 0.2 (IQR 0.3) to 0.06 (IQR 0.1) g/mmol (p < 0.01). Among the patients, eight (13.3%) were DD and 52 (86.7%) were non-DD genotypes (Table II). The non-DD genotype consisted of 29 (55. 8%) II patients and 23 (44.2%) ID patients. Although serum creatinine, eGFR, UPCI and serum cholesterol were not significantly different at the time of first presentation, the DD genotype patients had higher serum creatinine (178 [IQR 31.3] vs. 79 [IQR 88.3] μmol/L; p = 0.007), greater urinary protein (UPCI of 0.09 [IQR 0.2] vs. 0.04 [IQR 0.10] g/mmol; p = 0.04) and higher cholesterol level (6.2 [IQR 1.4] vs. 5.01 [IQR 0.8] mmol/L, p = 0.03) at the recruitment time. Their eGFR was also significantly low (42.1 ± 31.1 vs. 76.6 ± 42.1 ml/min/1.73m^2, p = 0.03).

The mean arterial pressure (MAP) was not significantly different between the groups. The DD patients were found to have the highest total histology, glomerular sclerosis and vascular lesion score compared to the non-DD patients. The total histological score of the DD patients was 7 as compared to 5 and 4 for ID and II, respectively. The vascular lesion score was the only finding which was significantly different among the DD and non-DD patients (score 2 vs. score 1). 80% of the DD patients had a vascular lesion score ≥ 2 as compared to 30.6% among the non-DD patients (p = 0.05).

Furthermore, the DD genotype patients had progressive disease, with lower eGFR during the recruitment time ($p = 0.03$), compared to the non-DD patients (Fig. 1). However, the annual renal function deterioration rate was not statistically significant. The DD group deteriorated at 5.7 ± 2.2 ml/min/1.73m^2/year, while the non-DD group at 4.8 ± 2.0 ml/min/1.73m^2/year ($p > 0.05$), and choice of medication was also the same for both groups.

Of all the patients, 49 (81.7%) had stable renal function (Group 1) while 11 (18.3%) had renal function deterioration (Group 2), of which six of them showed a doubling in serum creatinine (Table III). Group 2 patients had higher systolic blood pressure (144.2 [IQR 25.0] vs. 129.0 [IQR 16.7] mmHg; $p = 0.02$) and greater urinary protein excretion (UPCI 0.16 [IQR 0.1] vs. 0.05 [IQR 0.09]; $p = 0.03$) compared to group 1. They also had been followed-up for a longer period than those in group 1 (5.5 [IQR 15.4] vs. 3.8 [IQR 3.2] years; $p = 0.04$).

DISCUSSION

The DD genotype is not uncommon in our patients. It was noted in 13.3%, and both Yoshida et al and Lau et al identified 10%–15% DD genotype in their study patients.[10,15] It was showed that the DD genotype is strongly associated with poor disease progression compared to the non-DD genotype. Although the same finding was noted in a few studies from Italy and Singapore, Lau et al (2002) and Schene et al (2001) failed to reproduce the results, which could be due to the difference in the study populations.[16-18] Although genetic and environmental factors had been found to be involved in the disease onset, progression and outcome, multiple gene interaction is more important than the isolated gene determinations. For instance, the interaction between uteroglobin gene or gene variant T235 and ACE gene polymorphism had been shown to determine the disease progression significantly.[19] In their study, Firmat et al found that the DD genotype patients had higher tissue ACE concentration,[20] and our finding of severe vascular damages in the DD patients, despite their equal systemic mean MAP, supports the finding indirectly. Elevated tissue ACE concentration probably predisposed the patients to a higher intraglomerular pressure and severe vascular lesion.

This study demonstrated that the DD genotype may have adversely affected the disease progression of our local IgAN patients. It also identified elevated systolic blood pressure, significant proteinuria and long-standing disease as the significant prognostic factors. However, appropriate treatment strategies, especially strict blood pressure control and reduction in proteinuria with renin-angiotensin-aldosterone system (RAAS) blockade, protein restriction and adequate management of hypercholesterolaemia, delayed the disease progression. Although the DD genotype polymorphism was associated with poor disease progression, their response to the ACEIs was superior compared to the non-DD genotype polymorphism, as confirmed by an earlier study.[10]

More than 80% of our patients were treated with ACEIs or ARBs either for hypertension and/or proteinuria. Kanno et al demonstrated that the ACEIs improved the disease progression, regardless of their chronic histopathological changes.[21] Although the beneficial effects of ACEI and ARB combination are still inconclusive, its efficacy in IgAN patients had been demonstrated by the COOPERATE study group recently,[22] and 8% of our patients had received combination therapy. We believe that early presentation, mild histological lesion, widespread use of RAAS blockade had stabilised our IgAN patients, especially the DD genotypes. Furthermore, aggressive treatment for those with severe nephrosis or crescentic glomerulopathy is the other reason for stable study patients. Their treatment was intensified with the use of immunosuppressant and prolonged course of oral corticosteroid. Fish oil was used as an adjunctive therapy in almost half of our patients, and both local as well as international studies had proved its benefit in improving the degree of kidney inflammations.[23,24] The next commonest adjunctive therapy was dipyridamole, followed by aspirin, and most of them tolerated the treatment well.

This study had a few limitations which had affected its outcome; viz. a small number of study patients and short follow-up period. At least 10–15 years of follow-up is required to demonstrate the true association between ACE gene polymorphism, disease progression and treatment response in our IgAN patients. A subsequent large, well- randomised, prospective study is required to define the true association between ACE gene genotypes and disease progression in local IgAN patients. In conclusion, this study demonstrated that the frequency of our IgAN patients with DD genotype is 13% and it is probably associated with poor disease progression and renal prognosis. Other poor prognostic factors include higher systolic blood pressure, greater proteinuria and prolonged disease duration. However, treatment measures, especially RAAS blockade with ACEIs or ARBs, are effective to retard the disease progression. Hence, ACE gene polymorphism determination in any IgAN patient is not required in the daily clinical practice.

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