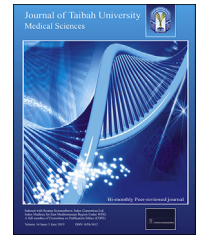




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Original Article

Association of angiotensin-converting enzyme G2350A gene polymorphisms with hypertension among patients with intracerebral haemorrhage

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المخلص

أهداف البحث: لتقييم علاقة الإنزيم المحول للأنجيوتنسين المتعدد الأشكال الجينية مع ارتفاع ضغط الدم، وحجم الورم الدموي داخل المخ، ومستوى الوعي، ونتيجة المرض بين المرضى المصابين بنزف داخل المخ.

طرق البحث: أجريت دراسة مقطعية عرضية في مستشفى زين العابدين العام خلال الفترة من مايو ٢٠١٦ إلى يونيو ٢٠١٧. استخدم تفاعل البلمرة المتسلسل للحصول على التركيب الوراثي للإنزيم المحول للأنجيوتنسين المتعدد الأشكال الجينية. كما تم تقييم حجم الورم الدموي داخل المخ باستخدام صيغة تقدير الحجم. وتم تقييم مستوى الوعي بواسطة مقياس جلاسجو للوعي. وتقييم نتيجة المرض باستخدام مقياس جلاسجو للنتائج. وتحليل اختبار العلاقة للتركيب الوراثي مع حالة ارتفاع ضغط الدم، وحجم الورم الدموي داخل المخ، ومقياس جلاسجو للوعي، ومقياس جلاسجو للنتائج للحالات المصابة بنزف داخل المخ باستخدام الانحدار اللوجستي المتعدد.

النتائج: تضمنت الدراسة ما مجموعه ٧٥ مريضاً بنزف داخل المخ. من هؤلاء، ٥٩ مريضاً مصاباً بارتفاع ضغط الدم، و٢٤ مريضاً لديه حجم الورم الدموي داخل المخ ≤ 60 سنتيمتراً مكعباً، و١٦ مريضاً لديه مقياس جلاسجو للوعي ≥ 8 ، و٧٢ مريضاً لديه مقياس جلاسجو للنتائج ٣-١. أظهرت نتائجنا أن الجين للإنزيم المحول للأنجيوتنسين المتعدد الأشكال الجينية كان مرتبطاً بشكل كبير بزيادة ارتفاع ضغط الدم ب ٣.٦ مرة، ولكن ليس مع حجم الورم الدموي داخل

المخ، ومستوى الوعي، ونتيجة المرض بين المرضى المصابين بنزف داخل المخ.

الاستنتاجات: الجين للإنزيم المحول للأنجيوتنسين المتعدد الأشكال الجينية يرتبط بارتفاع ضغط الدم عند المرضى المصابين بنزف داخل المخ.

الكلمات المفتاحية: نزف داخل المخ؛ ارتفاع ضغط الدم؛ الجين للإنزيم المحول للأنجيوتنسين المتعدد الأشكال الجينية

Abstract

Objectives: To evaluate the correlation of angiotensin-converting enzyme (ACE) G2350A gene polymorphisms with hypertension, brain hematoma volume (BHV), level of consciousness, and disease outcome among intracerebral haemorrhage (ICH) patients.

Methods: A cross-sectional study was conducted in Zainoel Abidin General Hospital from May 2016 to June 2017. Polymerase chain reaction was used to genotype ACE G2350A gene polymorphisms. BHV was assessed using the ABC/2 volume estimation formula. Level of consciousness was assessed by Glasgow coma scale (GCS). Disease outcome was assessed using Glasgow outcome scale (GOS). Association tests for ACE G2350A genotype in the context of hypertension status, BHV, GCS score, and GOS score in subjects with ICH was analysed by multiple logistic regression.

Results: A total of 75 ICH patients were included in the study. Of those, 59 patients exhibited hypertension, 24 patients had BHV ≥ 60 cm³, 16 patients possessed GCS

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scores ≤ 8 , and 72 patients had GOS scores of 1–3. Our analysis determined that the A allele of the ACE G2350A gene polymorphism was significantly associated with a 3.6-fold increase in hypertension; however, this polymorphism was not associated with BHV, level of consciousness, and disease outcome among ICH patients.

Conclusion: The A allele of the ACE G2350A gene polymorphisms is associated with hypertension among ICH patients.

Keywords: ACE G2350A gene polymorphism; Hypertension; Intracerebral haemorrhage

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Introduction

Intracerebral haemorrhage (ICH), the second most common sub-type of stroke, is a devastating critical disease associated with the highest morbidity and mortality of all stroke sub-types.^{1,2} Serious morbidity and mortality of ICH had been reported, where it was revealed that more than one third of patients with ICH did not survive, and functional independence was regained by only approximately 20% of the patients.³ The morbidity rate of ICH varies, ranging from 22.9 to 51.8 per 100 000 population,² and the mortality rate (the 30-day mortality rate) ranges from 35% to 52% of all ICH patients.⁴ The high mortality rate observed for ICH is triggered by several factors including hypertension,⁵ brain hematoma volume (BHV),⁶ level of consciousness, and disease outcome.⁷ Of these factors, it has been suggested that hypertension plays a central role in affecting the other factors. In the pathophysiology of ICH, higher blood pressure is directly proportional to larger BHV,⁸ and this pathological state has a crucial impact on decreased consciousness and poor prognosis in ICH patients.⁹ Additionally, a recent study found that hypertension was considered the main predictor for in-hospital mortality among ICH patients.⁵

In the pathogenesis of hypertension, it has been disclosed that angiotensin-converting enzyme (ACE) plays an important role in the renin-angiotensin-aldosterone system (RAAS) to cause vasoconstriction. In the RAAS, angiotensinogen is cleaved by renin into angiotensin I, and angiotensin I is subsequently cleaved into angiotensin II by ACE. Angiotensin II mainly affects the RAAS, where it induces vasoconstriction, sodium retention, and proliferative effects. These mechanisms are the forerunners for the development of hypertension.^{10,11} Therefore, it has been hypothesized that ACE may possess a potential correlation with these aggravating factors that include hypertension, BHV, level of consciousness, and disease outcome among ICH patients. The ACE G2350A gene is one of ACE genes that play a significant role in determining the ACE level within the circulation.¹² Therefore, our study aimed to

evaluate the association of ACE G2350A gene polymorphisms with hypertension, BHV, level of consciousness, and disease outcome among patients with ICH.

Materials and Methods

Study designs and patients

From May 2016 to June 2017, a cross-sectional study was conducted in Zainoel Abidin General Hospital, Banda Aceh, Indonesia to evaluate the correlation of ACE G2350A gene polymorphism with hypertension, level of consciousness, disease outcome, and BHV among patients with ICH. All enrolled ICH patients were treated in our Hospital, and all patients were Acehese, which is one of the ethnic groups in Indonesia. To confirm the diagnosis of ICH, brain computed tomography (CT) scans (Dual Source CT Scanner, Siemens Healthcare, Erlangen, Germany) was performed on all patients with clinical conditions and neurological examination related to ICH.¹³ Blood pressure (supine), performed at least three times, was measured after the patients had rested for at least 15 min using both a blood pressure monitor and an auscultatory method.¹⁴ The hypertension diagnosis was assessed using standard criteria formulated by the Joint National Committee VII.¹⁵ BHV was measured using the ABC/2 volume estimation as described by previous studies.^{16,17} Additionally, Glasgow coma scale (GCS) score was used to evaluate level of consciousness,¹⁸ and disease outcome was determined using Glasgow outcome scale (GOS) score.¹⁹ Patients experiencing severe infection, abnormal blood electrolyte levels, patients with ICH related to trauma, neoplasms, coagulation disorders or thrombolytic therapy, aneurysms, or other vascular malformations were excluded.

Genotyping of ACE G2350A gene polymorphism

Blood samples were collected in 10 ml Natrium - Ethylenediaminetetraacetic acid (Na-EDTA) tubes and kept frozen at -20°C . DNA was extracted using standard protocols adapted from previous studies.^{11,20–22} A set of primers (forward 5'-CTGACGAATGTGATGGCCGC-3' and reverse 5'-TTGATGAGTTCCACGTATT TCG-3') was designed to cover the polymorphic region of the ACE G2350A gene. A thermal cycler (Perkin Elmer 2400, Boston, USA) was used to amplify the DNA. A 10 mL total reaction volume contained 100–200 ng DNA templates, 125 mM dNTPs, 2.5 mM MgCl₂, 0.3 mM primers, and 1U Taq polymerase. DNA was amplified for 35 cycles, and each cycle consisted of pre-denaturation at 95 °C for 5 min, denaturation at 94 °C for 30 s, annealing at 58 °C for 30 s, extension at 72 °C for 30 s, and post-extension at 72 °C for 10 min. DNA sequencing was performed using BioEdit software (BioEdit, Carlsbad, USA). A fast digest BstU1 (Thermo Fisher Scientific, Waltham, USA) was used to digest the PCR products. We used 2% agarose gel (Hoeffer, Holliston, USA) to separate the digested fragments, and digested fragments were identified using ethidium bromide staining under ultraviolet transillumination. A 122-bp fragment was visualized as allele G2350, 100-bp and 22-

bp fragments were visualised as allele A2350, and 122–100 and 22 bp were visualised as the GA genotype.

Statistical analysis

The association of ACE G2350A gene polymorphism with hypertension, level of consciousness, disease outcome, and BHV among patients with ICH was analysed using multiple logistic regression. All significance tests were two tailed, and P-values of <0.05 were considered statistically significant. Statistical Package of Social Sciences 17.0 software (SPSS Inc., Chicago, IL) was used to analyse the data.

Results

During the study period, a total of 75 ICH patients were recruited for the study. Of those, hypertension was observed in 59 patients. The mean age for the normotension group was 54.50 years, and for hypertension group the mean age was 55.88 years. Approximately 56.25% and 52.54% patients were male for the normotension and the hypertension group, respectively. Other baseline characteristics of the patients included in our study are described in Table 1. Our analysis

found that the baseline characteristics between the normotension and the hypertension groups were not significantly different ($P > 0.05$), and therefore, our data were considered homogeneous.

Table 2 shows the distributions of the genotypes frequencies of ACE G2350A gene polymorphisms in the normotension and the hypertension groups. The genotype frequencies were 81.25% for GG, 18.75% for GA, 0% for AA in patients with normotension, and they were 49.15% for GG, 47.46% for GA, and 3.39% for AA in subjects exhibiting hypertension. For the allele frequencies, approximately 90.63% for G and 9.38% for A were observed in the normotension group, and 72.88% and 27.12% for the G and the A allele, respectively, were observed in hypertension group. Our analysis found that the A allele was associated with a 3.60-fold increased risk for hypertension among ICH patients.

The distributions of genotype frequencies of ACE G2350A gene polymorphisms for GCS ≤ 8 and GCS ≥ 9 are described in Table 3. The genotype frequencies were 56.25%, 43.75%, and 0.00% for GG, GA, and AA respectively in patients exhibiting a GCS ≤ 8 . For patients with a GCS ≥ 9 , the frequencies for GG, GA, and AA were 55.93%, 40.68%, and 3.39%, respectively. Our analysis found no

Table 1: Baseline characteristics of the patients included in this study.

Baseline characteristics	Normotension/Normotensive (n = 16)	Hypertension (n = 59)	p
Age (years)	54.50 \pm 11.08	55.88 \pm 12.16	0.852
Male	9 (56.25)	31 (52.54)	0.983
Hemoglobin (gr/dl)	12.27 \pm 2.61	12.43 \pm 2.40	0.875
Leukocyte(*10 ³ / μ l)	8.90 \pm 2.83	8.80 \pm 2.77	0.922
Thrombocyte (*10 ³ / μ l)	252.06 \pm 70.49	245.25 \pm 68.87	0.901
Urea (mg/dl)	34.00 \pm 11.68	33.63 \pm 9.15	0.259
Creatinine (mg/dl)	0.91 \pm 0.09	0.94 \pm 0.08	0.224
Total cholesterol (mg/dl)	190.56 \pm 25.45	197.27 \pm 16.70	0.331
HDL (mg/dl)	37.88 \pm 8.50	41.92 \pm 7.86	0.398
LDL (mg/dl)	122.38 \pm 46.13	143.17 \pm 43.89	0.224
Triglyceride (mg/dl)	178.94 \pm 16.97	188.02 \pm 18.70	0.164
Blood glucose (mg/dl)	150.00 \pm 19.62	142.29 \pm 29.41	0.893

Notes; Data were presented as mean \pm SD or n (%); HDL, high-density lipoprotein; LDL, low-density lipoprotein; OR, odds ratio; CI, confidence interval; SD, standard deviation.

Table 2: Genotypes and allele frequencies of ACE G2350 gene polymorphisms in hypertensive subjects among ICH patients.

Genotypes and alleles	Normotension (n = 16)	Hypertension (n = 59)	OR (95%CI)	p
GG vs. GA+AA	13 (81.25)	29 (49.15)	0.22 (0.06–0.87)	0.030
GA vs. GG+AA	3 (18.75)	28 (47.46)	3.91 (1.01–15.18)	0.048
AA vs. GG+GA	0 (0.00)	2 (3.39)	1.44 (0.07–31.39)	0.819
G vs. A	29 (90.63)	86 (72.88)	0.28 (0.08–0.98)	0.046
A vs. G	3 (9.38)	32 (27.12)	3.60 (0.41–2.43)	0.046

Notes; Data were presented as n (%); ACE, angiotensin-converting enzyme; ICH, intracerebral hemorrhage; OR, odds ratio; CI, confidence interval.

Table 3: The association between genotypes and allele frequencies of ACE G2350 gene polymorphisms and level of consciousness among ICH patients.

Genotypes and alleles	GCS ≤ 8 (n = 16)	GCS ≥ 9 (n = 59)	OR (95%CI)	p
GG vs. GA+AA	9 (56.25)	33 (55.93)	1.01 (0.33–3.08)	0.982
GA vs. GG+AA	7 (43.75)	24 (40.68)	1.13 (0.37–3.46)	0.825
AA vs. GG+GA	0 (0.00)	2 (3.39)	0.70 (0.03–15.25)	0.819
G vs. A	25 (78.13)	90 (76.27)	1.11 (0.43–2.84)	0.826
A vs. G	7 (21.87)	28 (23.73)	0.90 (0.35–2.30)	0.826

Notes; Data were presented as n (%); ACE, angiotensin-converting enzyme; ICH, intracerebral hemorrhage; GCS, glagow coma scale; OR, odds ratio; CI, confidence interval.

Table 4: The association between genotypes and alleles frequencies of ACE G2350 gene polymorphisms and glasgow outcome scale among ICH patients.

Genotypes and alleles	GOS 1–3 (n = 72)	GOS 4–5 (n = 3)	OR (95%CI)	P
GG vs. GA+AA	40 (55.56)	2 (66.67)	0.63 (0.05–7.21)	0.706
GA vs. GG+AA	30 (41.67)	1 (33.33)	1.43 (0.12–16.48)	0.775
AA vs. GG+GA	2 (2.78)	0 (0.00)	0.25 (0.01–6.22)	0.396
G vs. A	110 (76.39)	5 (83.33)	0.65 (0.07–5.73)	0.696
A vs. G	34 (23.61)	1 (16.67)	1.55 (0.17–13.68)	0.696

Notes; Data were presented as n (%); ACE, angiotensin-converting enzyme; ICH, intracerebral hemorrhage; GOS, glasgow outcome scale; OR, odds ratio; CI, confidence interval.

Table 5: The association between genotypes and alleles frequencies of ACE G2350 gene polymorphisms and brain hematoma volume among ICH patients.

Genotypes and alleles	BHV0-60 cm ³ (n = 51)	BHV ≥ 61 cm ³ (n = 24)	OR (95%CI)	P
GG vs. GA+AA	30 (58.82)	12 (50.00)	0.70 (0.26–1.86)	0.474
GA vs. GG+AA	19 (37.25)	12 (50.00)	1.68 (0.63–4.49)	0.298
AA vs. GG+GA	2 (3.92)	0 (0.00)	0.40 (0.02–8.75)	0.564
G vs. A	79 (77.45)	36 (75.00)	0.87 (0.39–1.95)	0.741
A vs. G	23 (22.55)	12 (25.00)	1.15 (0.51–2.55)	0.741

Notes; Data were presented as n (%); ACE, angiotensin-converting enzyme; ICH, intracerebral hemorrhage; BHV, brain hematoma volume; OR, odds ratio; CI, confidence interval.

association between level of consciousness and ACE G2350A gene polymorphisms among ICH patients.

We summarize the genotype frequencies of ACE G2350A gene polymorphisms in patients with GOS of 1–3 and GOS of 4–5 in Table 4. The genotype frequencies for patients with GOS of 1–3 were 55.56% for GG, 41.67% for GA, and 2.78% for AA. For patients with GOS of 4–5, the frequencies were 66.67%, 33.33%, and 0.00% for GG, GA, and AA, respectively. Our findings indicated no

association between GOS and ACE G2350A gene polymorphisms among ICH patients.

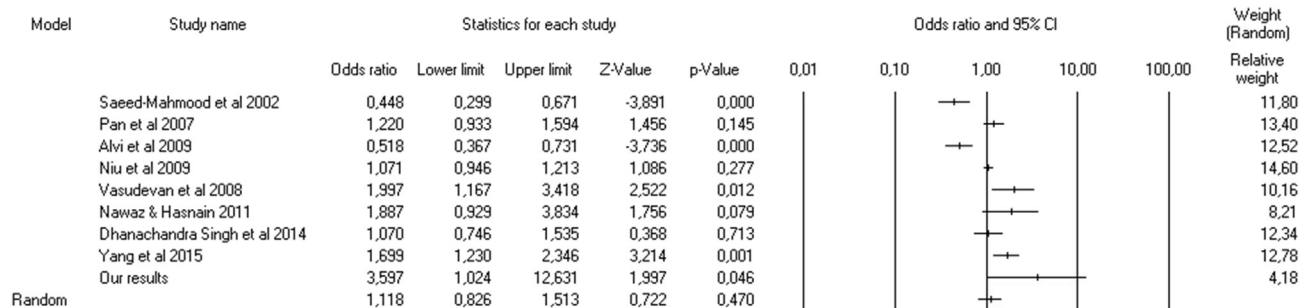
Table 5 summarizes the genotype frequencies of ACE G2350A gene polymorphisms in patients with BHV of 0–60 and BHV >60. We observed 58.82% for GG, 37.25% for GA, and 3.92% for AA in patients with BHV of 0–60. For BHV >60, the frequencies for GG, GA, and AA were 50.00%, 50.00%, and 0.00%, respectively. Our analysis found no association between BHV and ACE G2350A gene polymorphisms among ICH patients.

Discussion

It is widely established that ICH patients have widely varying prognoses, and these are influenced by several factors including hypertension, level of consciousness, disease outcome, and BHV. In addition to the factors, genetic polymorphisms may also play a crucial role in determining ICH prognosis. Our study reported the correlation of ACE G2350A gene polymorphisms with the risk of hypertension, level of consciousness, disease outcome, and BHV among patients with ICH.

Our results indicated that the A allele of ACE G2350A gene polymorphisms was associated with an increased risk for hypertension among patients with ICH. It has been reported that hypertension plays a crucial role in the development of ICH,²³ and the pathogenesis of hypertension is closely influenced by ACE.²⁴ Hypertension is a pathological state characterized by narrowing of the arteriolar lumen.²⁵ This abnormality is closely related to vasoconstriction and vascular hypertrophy. This narrowing of the arteriolar lumen may occur due to complex mechanisms involving the autonomic nervous system and both circulating and local vasoconstrictors including ACE.²⁶ It has been reported that ACE plays an important role in influencing the levels of the potent vasoconstrictor angiotensin II. In hypertension, angiotensin II, through various mechanisms, leads to direct vasoconstriction of precapillary arterioles and post-capillary venules and stimulates hypertrophy of vascular smooth muscle cells.²⁷ This mechanism may explain the correlation between hypertension and ACE G2350A gene polymorphisms among ICH patients as reported in our results.

Until now, no study reports the influence of ACE G2350A gene polymorphisms in hypertensive subjects with ICH. Therefore, we could not compare our results systematically with the results of previous studies. Previous studies have only reported the correlation between ACE G2350A gene

**Figure 1:** Forest plot of the association between ACE G.

polymorphisms and hypertension. Of those, four studies^{20,28–30} found that ACE G2350A gene polymorphisms were associated with the risk of hypertension, and in contrast, four other studies^{31–34} indicated no association. We attempted to combine the data from those previous studies with our data, and our pooled calculation found that ACE G2350A gene polymorphisms were not associated with the risk of hypertension (Figure 1). The results of our pooled calculation were contrary to those of a previous meta-analysis.¹² This previous study found that the A allele was associated with a protective effect against the risk of hypertension; however, data discrepancies between the report and the references were observed in the meta-analysis. Therefore, the accuracy of the meta-analysis is still in doubt. In the near future, we expect that there will be a meta-analysis report involving a larger and more accurate data set.

The prognosis of ICH patients is influenced by several aggravating factors including BHV, level of consciousness, and disease outcome. Although it is difficult to describe the exact mechanism regarding the association between ACE and these aggravating factors, there is an assumption that a linear correlation may exist between ACE and these aggravating factors. Elevated BHV scores usually lead to a decreased level of consciousness as a result of increased intracranial pressure, and this condition is associated with a poor prognosis⁹ and low GOS score.^{35,36} Indeed, BHV was considered more important than GCS in determining the treatment option in patients with ICH.³⁷ Additionally, a large BHV was demonstrated to be associated with elevated blood pressure,³⁸ and hypertension was shown to correlate with ACE G2350A gene polymorphisms.^{20,28–30} This suggested that ACE G2350A gene polymorphisms should have an impact on BHV and other aggravating factors; however, our study failed to show a correlation between these aggravating factors and ACE G2350A gene polymorphisms. These results are puzzling, and the absence of a clear correlation theory may be the main reason for these results. Additionally, the currently existing assumption was based solely on the low rational possibilities. In addition, no study reports the correlation between ACE and these aggravating factors among patients with ICH. This may explain the existence of no correlation between ACE G2350A gene polymorphisms and several aggravating factors including BHV, level of consciousness, and disease outcome as reported in our results.

There were several limitations in our current study. First, several precipitating factors including smoking status, alcohol consumption, and the use of sympathomimetic drugs were not included in the study. Second, false positive findings may occur due to small sample size. Third, our samples were only recruited from a single centre, and therefore the bias probability could not be ruled out.

Conclusions

In our population, the A allele of ACE G2350A gene polymorphisms is associated with increased risk for hypertension among ICH patients, and ACE G2350A gene polymorphisms exhibit no significant correlation with BHV, level of consciousness, and disease outcome. Our results provide the first evidence concerning ACE G2350A gene polymorphisms in hypertensive subjects with ICH.

Source of funding

There is no external funding for our study.

Conflict of interest

The authors have no conflict of interest to declare.

Ethical approval

The study was approved by the Institutional Review Board of Universitas Syiah Kuala, Banda Aceh, Indonesia (No. 039/KE/FK/2016) in accordance with the Declaration of Helsinki. All subjects and/or their family provided written informed consent prior to participation in this study.

Authors' contributions

Idea/concept: II. Design: II; SS. Control/supervision: II; SS; SS. Data collection/processing: II; SS; SS; FF; NM; JKF. Extraction/Analysis/interpretation: II; SS; SS; FF; NM; JKF. Literature review: II; JKF. Writing the article: II; JKF. Critical review: II; SS; JKF. All authors have critically reviewed and approved the final draft and are responsible for the content and similarity index of the manuscript.

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