









Association of SCN1A Gene Polymorphism with Phenytoin Response in Patients with Epilepsy: Relevance of Stratification by the History of Febrile Seizure

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Abstract

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AIM: The SCN1A gene encodes the NaV1.1 sodium channel in the central nervous system that serves as the target for phenytoin. Our study aimed to investigate the association of SCN1A polymorphism (SNP rs3812718) with phenytoin response.

MATERIALS AND METHODS: A total of 120 epileptic patients who had received phenytoin for at least 1 year were enrolled in the study and genotyped using the TaqMan assay. They were classified into phenytoin-responsive (n = 62) and phenytoin unresponsive groups (n = 58). Patients were also stratified according to the history of febrile seizure (24 in the febrile seizure subgroup; 96 patients in the no history of febrile seizure subgroup) and epilepsy etiology (47 in idiopathic; 73 in the symptomatic + cryptogenic subgroup).

RESULTS: The frequency of AA (19% vs. 11.3%) and AG genotypes (43.1% vs. 40.3%) was found to be more frequent in phenytoin unresponsive. GG genotypes dominated in the phenytoin responsive group (37.9% vs. 48.4%) but were not statistically significant (p > 0.05). We identified two variables associated with phenytoin response: the etiology of epilepsy (p = 0.012) and history of febrile seizure (0.014). A significant positive association between the rs3812718 genotype and phenytoin response was found when patients were stratified by a history of febrile seizures. In patients without a history of febrile seizures, the AA genotype had a higher risk of phenytoin unresponsiveness than the GG genotype (p = 0.048; OR 3.73, 95% CI: 1.01–13.78).

CONCLUSION: There was no significant association between the rs3812718 polymorphism and phenytoin responsiveness in patients with epilepsy. In the patients without a history of febrile seizure subgroup, AA increased the risk of phenytoin unresponsiveness compared to the GG genotype.

Introduction

Epilepsy is a common, chronic, and complicated yet controllable neurological disease. The majority (up to 60–70%) of patients with epilepsy become seizure-free after receiving appropriate pharmacological treatment with anti-epileptic drugs (AED), and most of them have their epilepsy controlled with a single use of AED (AED monotherapy). Several adjustments to the AED regimen, including AED substitution or multiple AED combinations (AED polytherapy), are still needed to achieve epileptic control in about one-third of patients with epilepsy. Uncontrolled epilepsy has been associated with deterioration in patients' quality of life; also, the likelihood of achieving controlled epilepsy declines with the increased number of AEDs used [1], [2], [3].

The mechanisms of the development of drug-resistant epilepsy are still poorly understood. Since individuals respond to certain AEDs, it is thought

to be multifactorial, including several acquired and genetic variables. Genetic factors play a major role in the underlying etiology of epilepsy, modulating the susceptibility to an epileptogenic insult, and determining the pharmacokinetics and pharmacodynamics of AEDs [3], [4]. For instance, polymorphism in genes related to AED metabolism, transport, and targets may alter responses to AEDs either by reducing serum drug concentration and AED access to the epileptic focus in the central nervous system (CNS) or by making changes in AED targets [3]. Thus, findings in the pharmacogenetics field support an individualized or personalized therapy according to patients' unique genetic profiles [5].

The primary mechanism of most AEDs is the inhibition of voltage-gated sodium channels (VGSC). The mutations in genes encoding this channel may serve as an important factor in susceptibility to epilepsy, influencing responses to AEDs, including the development of AED resistance. VGSC is the principal target for many AEDs, including phenytoin.

Together with carbamazepine, phenytoin is widely prescribed worldwide due to its properties as a first-line AED for focal and generalized epilepsy and also affordability [3], [6], [7], [8], [9].

The VGSC responsible for regulating neural excitability has two subunits, namely, alpha and beta. The sodium voltage-gated channel alpha subunit 1 (SCN1A) gene encodes the alpha subunit of the Nav1.1 sodium channel in CNS neurons [10]. This channel initiates action potentials in neurons in various parts of the mammalian brain, namely, the hippocampus, thalamus, and cerebellum, which play a role in epilepsy [11]. SCN1A IVS5N+5 G->A or rs3812718 is a single nucleotide polymorphism (SNP) located in the 5' splice donor site. This frequent SNP disrupts the conserved consensus-site sequence and alters the proportions of the adult (5A) and neonatal form (5N) of exon 5 transcripts, making the encoded sodium channel altered in its functional properties. The G allele expressed both neonatal and adult forms equally, where A reduces the expression of the 5N form in relevance to 5A. Individuals with the AA genotype may have an undetectable level of the 5N form. The previous studies reported that Nav1.1 sodium channels containing exon 5N were more sensitive to phenytoin and required lower doses of phenytoin compared to those dominated by exon 5A. The resulting difference may have an impact on AED dosage requirements [8], [12], [13]. Remy declared that phenytoin and lamotrigine both promote greater inhibition of the Nav1.1-5N protein [14].

The first reported evidence revealed a significant correlation between rs3812718 polymorphism with the dosing of phenytoin and the serum level of phenytoin at maintenance dose in 2005 [8], [9]. This SNP has also been associated with carbamazepine resistance [15]. However, later studies have shown the opposite. A study by Zhou *et al.* demonstrated no significant association between rs3812718 polymorphism and AED resistance in all types of AEDs in Han Chinese populations [16]. Meanwhile, other studies by Manna *et al.* and Yun *et al.* also supported that the rs3812718 polymorphism was not associated with carbamazepine response and the development of resistance [17], [18]. Kumari *et al.* reported that rs3812718 was associated with the susceptibility to epilepsy but not with the therapeutic response of Carbamazepine/Oxcarbazepine in Northern Indian populations [19].

The conflicting results between existing studies gave rise to further studies regarding the association of SCN1A rs3812718 polymorphism with therapeutic responses in patients with epilepsy. Most of the studies published used carbamazepine, and the study of SNP association with phenytoin response is scarce, especially in the Indonesian population. Our study aimed to investigate the association of SCN1A polymorphism (SNP rs3812718) with phenytoin responses and stratification by the history of febrile seizure and the etiology of epilepsy.

Materials and Methods

The protocol for this case-control study was approved by the Medical and Health Research Ethics Committee of the Faculty of Medicine, Public Health and Nursing, Universitas Gadjah Mada, Yogyakarta, Indonesia. Participating subjects or their legal guardians signed a written informed consent form before participating in the study.

Study population

This study included 120 outpatients attending the neurology clinic at three general hospitals in Yogyakarta, Indonesia: Dr. Sardjito Hospital, PKU Gamping Hospital, and Bantul Hospital from December 2019 to March 2021. Patients with an established clinical diagnosis of epilepsy, according to the International league against epilepsy 2014 criteria, treated with phenytoin for at least 1 year, were recruited for this study. Other inclusion criteria included: (1) age >5 years; (2) epilepsy manifesting as convulsive seizures; and (3) frequency of seizure >4 times before phenytoin treatment. Patients with poor adherence to AED, pregnancy, a history of psychological non-epileptic seizure, a brain tumor, kidney failure, or chronic liver disease were all excluded from the study.

According to the following definitions, the subjects were classified into drug responsive (control) and unresponsive (case) groups. Drug responsiveness was defined as a decrease in seizure frequency (<4 times a year) after receiving phenytoin for at least 1 year. Meanwhile, unresponsiveness was defined as uncontrolled epilepsy with a seizure frequency of ≥ 4 times per year after a year of phenytoin treatment and/or receiving other additional AEDs due to uncontrolled epilepsy after the maximum dose of phenytoin.

Collection of clinical parameters

Neurologists obtained data regarding patients' characteristics and medical history on a specific form before genotyping. The list of data collected was the following: gender, weight and height, age of onset, seizure frequency before treatment (≤ 4 times, 5–10 times, or > 10 times), frequency of seizure in the past year (<4 times or ≥ 4 times), seizure types (focal or general), etiology of epilepsy (idiopathic, symptomatic, or cryptogenic), phenytoin dosing (≤ 200 mg per day or > 200 mg per day), additional AED beside phenytoin (monotherapy or polytherapy), history of stroke (yes or no), history of head trauma (yes or no), history of intracranial infection (yes or no), history of status epilepticus (yes or no), and history of febrile seizure (yes or no).

Genotyping

Blood samples of all subjects were collected during an outpatient visit, stored within an EDTA tube, and frozen at -80°C until extraction, which took approximately 2 days. According to the manufacturer's protocol, the genomic extraction was performed using a commercial kit (FavorPrep™ blood/cultured cell genomic DNA extraction mini kit, Favorgen Biotech Corp). Extracted DNA samples were genotyped for the c.603-91G>A (rs3812718) SNP (GeneBank: NM_001165963) using a custom-designed TaqMan-based allelic discrimination assay protocol (Applied Biosystems by Thermo Fisher, Foster City, CA, USA). Assay primers and fluorescent-labeled probe sequences used are listed in Table 1.

Table 1: Primer and probe sequences used in the assay

Primers and probes used	Sequence
Primer	
Forward	5'-TTTCAGAGTCTTGAGAGCTTTGAAAA-3'
Reverse	5'-TGTGACGTACCTGTAATAGGGAGTTC-3'
Probe	
A probe	VIC-AATTCCAGGTAAGTGA-MGB,
G probe	FAMAATTCCAGGTAAGAAGTGA-MGB

Polymerase chain reaction (PCR) was conducted in an Applied Biosystems 7500 Fast Instrument with the following conditions optimized for TaqMan genotyping assays. The PCR procedure consisted of 3 steps as follows: initial DNA polymerase activation step at 95°C for 20 s, followed by 40 cycles of denaturation at 95°C for 3 s, and final annealing or extending step for 40 cycles at 60°C for 30 s. Fluorescence outputs were visualized and quantified in real-time using an Applied Biosystems 7500 Fast Real-Time PCR System, and the data were analyzed using SDS software, version 2.3 (Applied Biosystems).

Statistical analysis

Statistical analysis was performed with STATA statistical analysis software, version 13. Hardy-Weinberg equilibrium (HWE) was conducted with Chi-square analysis test to identify any disequilibrium in genetic distribution. The association between SNP genotype and other related clinical parameters with drug response was calculated by Chi-square and Fisher exact tests. Clinical parameters included in the analysis were seizure onset, seizure type, etiology of epilepsy, history of stroke, head trauma history, status epilepticus, history of intracranial infection (meningoencephalitis/encephalitis), and history of febrile seizures. Associative associations were expressed as odds ratios (OR) or risk estimates with 95% confidence intervals (CI). $p < 0.05$ was considered as significant association.

Results

A total of 120 patients were enrolled in this study, 54.4% ($n = 68$) male and 41.6% ($n = 52$). All patients were

epileptic patients taking phenytoin; 62 patients (48.3%) and 58 patients (51.7%) were classified into phenytoin responsive and unresponsive, respectively. The genotype frequencies were 15% ($n = 18$) for AA, 42.5% ($n = 52$) for AG, and 41.7% ($n = 50$) for GG. There was no deviation from the HWE observed in the allelic frequency ($p = 0.287$). Table 2 presents the clinical characteristics of patients in each group. Patients in the case and control group were comparable in gender, age of seizure onset, seizure type, history of stroke, head trauma, intracranial infection, status epilepticus, and febrile seizure ($p < 0.005$). Idiopathic etiology of epilepsy was more frequent in the responsive group, while symptomatic and cryptogenic etiology was more frequent in the unresponsive group ($p = 0.012$). History of febrile seizure was also found to be associated with phenytoin unresponsiveness ($p = 0.014$).

Table 2: Characteristics of patients in the case and control group

Variables	Response to phenytoin		p
	Unresponsive n (%)	Responsive n (%)	
Gender			
Males	34 (58.6)	34 (54.8)	0.676 [#]
Females	24 (41.4)	28 (45.2)	
Age of onset			
≤ 25	33 (56.9)	42 (67.7)	0.220 [#]
> 25	25 (43.1)	20 (32.3)	
Seizure type			
Focal	30 (51.7)	23 (37.1)	0.107 [#]
General	28 (48.3)	39 (62.9)	
Epilepsy etiology			
Idiopathic	16 (27.6)	31 (50)	0.012 ^{#*}
Symptomatic+cryptogenic	42 (72.4)	31 (50)	
History of stroke			
Yes	12 (20.7)	11 (17.7)	0.682 [#]
No	46 (79.3)	51 (82.3)	
History of head trauma			
Yes	15 (25.9)	8 (12.9)	0.072 [#]
No	43 (74.1)	54 (87.1)	
History of intracranial infection			
Yes	10 (17.2)	4 (6.5)	0.066 [†]
No	48 (82.8)	58 (93.5)	
History of status epilepticus			
Yes	10 (17.2)	11 (17.7)	0.943 [#]
No	48 (82.8)	51 (82.3)	
History of febrile seizure			
Yes	17 (29.3)	7 (11.3)	0.014 ^{#*}
No	41 (70.7)	55 (88.7)	

*significant $p < 0.05$, [#]Chi-square, [†]Fisher exact test; CI: Confidence interval.

The AA and AG genotypes frequency was higher in the unresponsive group than the responsive group, 19% versus 11.3% for AA genotype, and 43.1% versus 40.3% for AG genotype, respectively. On the contrary, the GG genotype was more frequent in the responsive group (48.4%) compared to the non-responsive group (37.9%). The association between rs3812718 genotype with phenytoin response was assessed, and there was no significant correlation between genotype variants with phenytoin response (Table 3).

Table 3: Association between rs3812718 genotypes and phenytoin response

Genotype of Rs. 3812718	Phenytoin response		Statistical analysis	
	Unresponsive (n = 58) frequency (%)	Responsive (n = 62) frequency (%)	p	OR (95% CI)
AA	11 (19.0)	7 (11.3)	0.173 [#]	2.14 (0.72–6.41)
AG	25 (43.1)	25 (40.3)	0.436 [#]	1.36 (0.62–2.98)
GG	22 (37.9)	30 (48.4)	Reference	1.00

[#]Chi-square, CI: Confidence interval, OR: Odds ratio

The analysis was followed by stratification of patients according to epilepsy etiology and history of

Table 4: Genotype frequencies and the association between rs3812718 and drug response after stratified by epilepsy etiology and febrile seizure history

Subgroups based on stratification	Genotype	Phenytoin response		Statistical analysis		
		Unresponsive n (%)	Responsive n (%)	p	OR (95% CI)	
Epilepsy etiology	AA	3 (18.8)	3 (9.7)	0.341 [†]	2.43 (0.39–15.08)	
	AG	6 (37.5)	11 (35.5)	0.678 [#]	1.33 (0.35–5.00)	
	GG	7 (43.8)	17 (54.8)	Reference	1.00	
Symptomatic + cryptogenic	AA	8 (19.0)	4 (12.9)	0.445 [†]	1.73 (0.42–7.11)	
	AG	19 (45.2)	14 (45.2)	0.754 [#]	1.17 (0.43–3.24)	
	GG	15 (35.7)	13 (41.9)	Reference	1.00	
History of febrile seizure	Yes	AA	3 (17.6)	2 (28.6)	0.315 [†]	0.30 (0.03–3.14)
		AG	4 (23.5)	3 (42.9)	0.224 [†]	0.27 (0.03–2.25)
		GG	10 (58.8)	2 (28.6)	Reference	1.00
	No	AA	8 (19.5)	5 (9.1)	0.048 [#]	3.73 (1.01–13.78)
		AG	21 (51.2)	22 (40.0)	0.082 [#]	2.23 (0.90–5.49)
		GG	12 (29.3)	28 (50.9)	Reference	1.00

*significant p < 0.05, #Chi-square, †Fisher exact test, CI: Confidence interval, OR: Odds ratio.

febrile seizure (Table 4). Significant association between rs3812718 polymorphism and phenytoin response was found only in the subgroup of patients without history of febrile seizure. There were no significant associations in patients with a history of febrile seizure and subgroups stratified by epilepsy etiology (p > 0.05). In patients without history of febrile seizure, there was significant association between AA with phenytoin unresponsiveness (p = 0.048), suggesting that AA genotype increases the risk of phenytoin unresponsiveness by 3.73 times compared to GG (95% CI: 1.01–13.78). Clinically, the same trend was found in the AG versus GG genotype, where the AG genotype increases the risk of phenytoin unresponsiveness (OR 2.23, 95% CI: 0.90–5.49), but it was not statistically significant (p = 0.082).

Discussion

Because several clinical and genetic factors influence responses to AEDs and the development of AED resistance, our study aimed to analyze the association of both genetic polymorphism and several clinical factors with phenytoin responses. As reported by Tate et al. [9], SNP rs3812718 was chosen due to its importance in regulating SCN1A gene expression, and the SCN1A gene has been associated with phenytoin serum levels during maintenance dose, as reported by Tate et al. [9].

Our study demonstrates that AA and AG genotypes tended to be more frequent in patients who were unresponsive to phenytoin, while the GG genotype was more frequent in the responsive group. This finding corresponds to the theory that the A allele is less sensitive to phenytoin due to its greater expression of 5A compared to 5N exons [13]. There is limited evidence using phenytoin as a studied drug, but studies on carbamazepine show a similar trend. The identical genotype distributions were observed

in the study conducted by Abe et al., in which the AA genotype dominated in the carbamazepine resistance group (AA > AG > GA) [15]. Sterjev et al. revealed that the A allele was associated with a higher maintenance dose in carbamazepine-responsive patients [20].

However, we found no significant association between genotype distribution and phenytoin responses. The previous study in Northern Indian populations also failed to demonstrate a significant association between SNP rs3812718 and carbamazepine resistance [19]. In Han Chinese populations, there was no significant association between SNP rs3812718 and drug-resistant epilepsy [16]. The complexity of the drug response mechanism may contribute to the difficulty of demonstrating a significant association with SNP when analyzed as a whole group response without considering contributing clinical factors. However, a previous study by Baghel and his team found that the SNP rs2812718 AC haplotype and the rs6432860A-rs3812718C AC diplotype were linked to recurrent seizures in Northern Indian patients who took phenytoin monotherapy [21].

We hypothesized that the association of rs3812718 polymorphisms and responses to phenytoin might be modified by the presence of factors theoretically known to influence drug-resistant epilepsy. In the present study, the analysis of associated clinical parameters indicates that epilepsy etiology and febrile seizure history have a significant association with phenytoin response. We recommend performing further analysis on these significant factors on a stratification basis. In the stratification according to the history of febrile seizures, a significant association between the studied rs3812718 genotype and phenytoin response was found in the non-febrile seizure subgroup. In this subgroup, the AA genotype was significantly higher in the unresponsive group compared to the GG genotype (p = 0.048). No significant difference was found in the subgroup with a history of febrile seizures, and the larger subjects' proportions may explain this in the subgroup without a history of febrile seizures. The history of febrile seizures was associated with drug resistance based on its pathogenesis, contributing to hippocampal damage. Prolonged febrile seizures in infancy are also associated with severe damage to temporomandibular structures up to hippocampal sclerosis. The resulting structural abnormalities are the underlying etiology of resistance to AEDs.

The relationship between the history of febrile seizures and drug-resistant epilepsy is currently inconclusive. Several studies support the theory that a history of febrile seizures increases the risk of drug-resistant epilepsy, but others have shown conflicting results. Our findings are supported by a study conducted by Hitiris et al. in Scotland, showing that a history of febrile seizures was associated with

drug-resistant epilepsy [22]. Another study by Kwong *et al.* and also supported the history of febrile seizures as a predictor of drug-resistant epilepsy [23]. A meta-analysis by Kalilani *et al.* found that a history of febrile seizures increased the risk of drug-resistant epilepsy (pooled OR: 1.31, 95% CI: 1.02–1.68) [24]. Another meta-analysis by Xue-Ping *et al.* also identified a history of febrile seizures as a strong risk factor for drug-resistant epilepsy (RR 3.43, 95% CI: 1.95–6.02) [25]. The opposite result was found in a case–control study by Roy *et al.*, where a history of febrile seizures had no significant association with the incidence of drug-resistant epilepsy ($p = 0.93$) [26].

Many factors influence discrepancies between our findings and previous evidence. We only studied 1 SNP among other *SCN1A* gene polymorphisms. Other SNPs in the *SCN1A* gene, *SCN9A*, and other distant genes that interfere with drug metabolism or transport should be considered in future studies, because there is a probability of interaction between SNPs which may affect responses to treatment. Other factors that should be considered include the subject's ethnicity, previous treatment history, and duration of epilepsy. These *SCN1A* gene polymorphisms are closely related to ethnicity, and in Indonesia, there are many diverse ethnicities. People who have had epilepsy for a long time and who have had previous treatment are also thought to have different reactions to AEDs.

Another factor possibly related to the discrepancy in findings is differences in dosing strategies. When a certain AED fails to achieve seizure freedom, there is a tendency to perform AED substitution instead of increasing the dose of the current AED. Another limitation is that we also did not measure serum levels of phenytoin, which also contributed to treatment effectiveness. A larger sample is recommended for further studies with a broader accounting of dosing strategies, including the possibility of a cost-effective analysis with a pharmacokinetic population study.

Conclusion

Our study did not find a significant association between *SCN1A* rs3812718 and response to phenytoin. A significant association was found after stratification with history of febrile seizure, where AA genotype was associated with phenytoin unresponsiveness compared to GG genotype in subgroup of patients without history of febrile seizure ($p = 0.048$; OR 3.73, 95% CI: 1.01–13.78). The rs3812718 stratification analysis in the epilepsy etiology did not show a significant difference in response to phenytoin ($p > 0.05$).

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