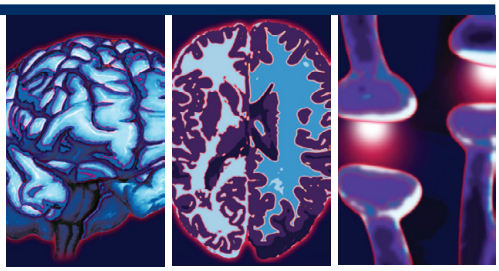
Research



The Polymorphisms of DRD2 141-C Ins/Del Receptor Influenced the Treatment Responses of Schizophrenia Patients

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ABSTRACT

Polymorphisms of DRD2 receptors lead to vary in the treatment responses of schizophrenia patients.

Objectives: This study carried out to know the association of polymorphisms of DRD2 141-C Del/Ins receptors to the doses needed of antipsychotic drug, length of hospital stay, and improvement of symptoms of schizophrenia patients.

Methods: The 208 of schizophrenia patients recruited in this study, was hospitalized and have given haloperidol (first generation of antipsychotic drug) then the treatment responses were evaluated by CGI score. The genotyping of the blood performed for DRD2 receptors polymorphisms.

Results: This study showed that DD genotype needed higher doses of antipsychotic drugs (p<0,05), have longer hospital stay (p<0,05), and have a minimum improvement of symptoms (p<0,05).

Conclusion: It was concluded that polymorphisms of DRD2 141-C Del/Ins receptors influenced the treatment responses and should be considered when treating schizophrenia patients with haloperidol.

Keywords

DRD2 receptors polymorphisms, Schizophrenia, Treatment responses

Introduction

Genetic factor was believed has a role in variation of treatment responses of antipsychotic drugs in schizophrenic patients [1-7]. However, many studies on DRD2 receptors polymorphisms as main target of antipsychotropic drugs revealed conflicting results [8-11]. The latest study with transcriptomics technology found that cluster genes of DRD2 community have a strong relation to schizophrenia risk [12].

The objectives of this study was to know the association of polymorphisms of DRD2 141-C Ins/Del receptors to the treatment responses such as doses needed of antipsychotic drugs, length of hospital stay, and improvement of symptoms of schizophrenia patients. Haloperidol (the first generation antipsychotic drugs) was studied since this drugs widely used in Mental Hospital for schizophrenia patients [13,14] and covered by national health insurance (BPJS) as well.

Methods

This study was carried out with 208 schizophrenia patients who recruited from the District Mental

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Hospital of South Sulawesi Province in Makassar Indonesia. The study was approved by Ethical Board of Medical Faculty of Hasanuddin University no UH.11060133.

■ Subjects

Schizophrenia patients diagnosed with DSM-IV criteria and were excluded if subjects had drug abuse history and organic mental disorder. Standard treatment given by hospital with normally used first generation antipsychotic drugs (haloperidol) which covered by health insurance. Clinical Global Impression (CGI) score for the schizophrenia patients was performed after 2 weeks treatment to determine the progress of treatment responses [15,16].

■ Genotyping

DNA was extracted from whole blood by standard protocol than genotyped *via* PCR-RFLP analysis. PCR was performed using primers as detailed by Arinamy et al. to amplify a 304 bp region [1]. Than for PCR-RFLP analysis in this study based on Schindler et al. techniques as follow [5]: The primers was used to amplify 75 ng DNA in a total volume of 10 µl (with 20 mM Tris-HCl, 10 mM KCl, 10 mM $(NH4)_2SO_4$,; 100 µg/ml BSA; 2 mM Mg; 0,1 Triton X-100, 250 µM dNTPs, 50 ng of each primer,0,625 units Pfu polymerase). Initial denaturation was carried out for 1 min at 98°C and was followed by 35 cycles of 98°C for 20 s and 74°C for 1 min; final extension was at 72°C for 7 min. The entire PCR product was digested with 5 units of BstNI enzyme and incubated at 37°C. Digestion products were separated on a 2,2% agarose stained with 0,5 µg/ml ethidium bromide and observed under ultraviolet light. Digestion of the 304-bp PCR product yielded two fragments of 160 and 144 bp for insertion (-141C Ins) allele whereas the PCR fragment of the deletion (-141C Del) allele remain undigested (304 bp).

■ Data Analysis

Polymorphisms of DRD2 141-C Ins/Del (DD, DI and II) was analyzed and determined the association of genotype to the doses of drugs, length of hospital stay, and response to treatment by chi-square statistical test.

Results

Our data showed **(Table 1)** that schizophrenia patient commonly have II genotype (54.3%) and more in men (72%), while control group commonly have DI genotype (91%). Patient with have DD genotype used higher doses of drugs (p<0,05) compare to DI and II genotype **(Table 2).**

Length of stay in hospital also more longer in DD genotype patients, compare to DI and II patients (p<0,05) as shown in **Table 3**. Improvement of the symptoms of DD genotype patients was worst (p<0,05), compare to DI and II genotype as well **(Table 4)**.

Discussion and Conclusion

This study revealed that polymorphisms of DRD2 141-C Ins/Del receptors could influence the doses of antipsychotic used. Schizophrenia patient with DD genotype need more doses of antipsychotic drugs (haloperidol) compare to DI and II genotype (p<0,05), indicating that this drugs did not effective to inhibited DRD2 receptors for DD genotype. This study in line with the study by Lencz et al. and Zhang JP et al. which found that DD genotype of schizophrenia patients used higher doses of antipsychotic drugs compare to DI and II genotype [17,18]. Inversely, II genotype had high density of DRD2 receptors which the main transmission of dopamine that could be inhibited by antipsychotic drugs effectively. Therefore in this study, II genotype patients need only a small doses of the drugs compared to DD genotype (p< 0,05). The underlying mechanisms was unclear, although density of D2 receptors was believed associated with DRD2 receptors Ins/Del polymorphisms [19].

Length of hospital stay also longer significantly in DD genotype patients compared to DI/II genotype patients **(Table 3)**, due to ineffectiveness of antipsychotic drugs. Improvement of symptoms by CGI score in DD genotype patients very minimal compared to other genotype (p<0,05), which also due to of ineffectiveness of the drugs.

as well **(Table 4)**. These data, in line with several study before, showed the association of DD genotype schizophrenia patients to have more length of hospital stay and minimum improvement of symptoms during treatment in the hospital [18,20,21].

The limitation of this study was the homogeneity of the schizophrenia patient, which not differentiated between acute and chronic patient which could be any alteration in sensitivity of DRD2 receptor from chronic patients. Another limitation was this study did

Table 1: Samples characteristic.

Variable	Subjects
	n=208
Age (yr)	36.62 ± 12.27
Sex	
Male	150 (72.2%)
Female	58 (27.8%)
DRD2 141C I/D polymorphisms	
DD	62 (29.8%)
DI	33 (15.9%)
II	113 (54.3%)
CGI-S	
Heavy illness (6)	88 (42.3%)
Very heavy illness (7)	120 (57.7%)

Table 2: The doses of antipsychotic used by schizophrenia patients based on DRD2 141-C I/D polymorphisms.

Doses		Genotype		p
	DD	DI	II	
High	34 (58.8%)	15 (45.5%)	25 (22.1%)	
Middle	14 (22.6%)	10 (30.3%)	45 (39.8%)	0,000
Low	14 (22.6%)	8 (24.2%)	43 (38.1%)	
Total	62 (100%)	33 (100%)	113 (100%)	
p=Chi-square test				

Table 3: The length of hospital stay of schizophrenia patients based on DRD2 141-C I/D polymorphisms.

Length of hospital stay		Genotype		p
	DD	DI	II	
>2 months	34 (54.8%)	17 (51.5%)	28 (24.8%)	
1-2 months	5 (8.1%)	7 (21.2%)	12 (10.6%)	0,000
<1 months	23 (37.1%)	9 (27.3%)	73 (64.6%)	
Total	63 (100%)	33 (100%)	113 (100%)	
p=Chi-square test				

Table 4: Improvement of the symptoms of schizophrenia patients after 2 weeks by CGI score based on DRD2 141-C I/D polymorphisms.

	Genotype			p
CGI-I score	DD	DI	II	
Minimum improvement (3)	41 (66.1%)	24 (72.7%)	38 (33.6%)	
Mild improvement (2)	21 (33.9%)	8 (3.0%)	60 (53.1%)	0.000
Maximum improvement(1)	0 (0.0%)	1 (3.0%)	15 (13.3%)	
Total	62 (100%)	33 (100%)	113 (100%)	
p : Chi-square test				

not determined polymorphisms in COMT and DAT receptors which play a significant role in dopamine transmission on schizophrenia patients [20-25]. However, this data revealed the facts that polymorphisms in DRD2 141-C Ins/Del receptors involved in treatment responses of schizophrenia patients when treated with haloperidol.

It is concluded that polymorphisms of DRD2 receptors influenced the treatment responses and should be considered when treating schizophrenia patients with haloperidol (first generation antipsychotic).

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Conflicts of Interest

The authors declare no conflict of interest.

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