Candidate IL-1β -511C/T Polymorphism in Schizophrenia Patients in Batak Tribe

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Abstract. Background: There are approximately 20 million cases of schizophrenia worldwide. This complication can result from developmental processes, neurodegenerative, and neurotransmitter disorders to the occurrence of infectious or autoimmune processes. Furthermore, serotonin, noradrenaline, dopamine, and glutamate are just a few of the neurotransmitters that cytokines may play a role in controlling. The relationships between glutamate and dopamine seem to be important for understanding the pathophysiology of schizophrenia. According to cellular receptors and the intracellular environment, which serve as risk factors for schizophrenia, IL-1 is involved in neurodevelopmental processes and can have neurotoxic or neuroprotective effects.

Method: Non-probability purposive sampling was conducted on 240 subjects (120 people with schizophrenia (ODS) and 120 healthy control of Batak tribe) hospitalized at Prof. M. ILDREM Medan, Indonesia, as normal control and East Medan Sub-district as healthy control. In addition, the IL-1β -511 C/T Polymorphism was analyzed using RFLP and PCR methods.

Result: The -511Allele frequency of the IL-β -511 C/T (rs16944) polymorphism was different between cases and controls with a p-value of 0.001 and OR of 1.901 and a 95% confidence interval between 1.322 to 2.735. The p-value for the genotype (CC vs. TT) was 0.019 with an OR of 0.414 and a 95% CI between 0.198–0.866. Meanwhile, the p-value for the genotype (CT vs TT) was 0.388 with an OR of 0.746 and a 95% CI between 0.384–1.451.

Conclusion: The results showed that the IL-1β -511 C/T polymorphism has a relationship with the incidence of schizophrenia, and may be a risk factor for schizophrenia in Batak people.

Keywords: schizophrenia · variant · interleukin-1β · interleukin-2 · Bataknese · control

1 Introduction

Schizophrenia is found in approximately 20 million people worldwide but is not the most common among other mental disorders. It occurs earlier in men [1] and is a complex disorder influenced by genes with mild to moderate effects and non-genetic risks such as environmental and psychological factors that alter the chemical structure of the brain.

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Many theories were proposed as risk factors for schizophrenia, starting from developmental processes, neurodegenerative, and neurotransmitter disorders to the occurrence of infectious or autoimmune processes [2]. Growth factors and other cytokines have been linked to the pathology or genesis of schizophrenia, and it has been found that the central nervous system contains and utilizes their receptors (CNS). These include the cytokines tumor necrosis factor (TNF), interferon (IFN), interleukin 1 (IL1), IL2, IL3, IL4, IL6, IL10, IL12, IL-15, and IL-18, as well as growth factors such as the transforming growth factor (TGF), macrophage colony-stimulating factor (M-CSF), platelet-derived growth factor (PDG), epidermal growth factor (EGF), fibroblast growth factor (FGF),etc. [3, 4]

Cytokines are polypeptides and glycosylated monomeric or polymeric proteins that are the result of numerous genes. Dimers (homodimers or heterodimers) and trimers are the most prevalent types (homotrimers and heterotrimers). Although numerous cell types produce cytokines, T helper (Th) cells and macrophages are the main producers. They can be created during physiological and pathological events in and by peripheral nerve tissue. Additionally, cytokines can influence endocrine, paracrine, and autocrine cells [4, 5]. They boost the production of other cytokines like IL-1, which causes the release of IL-2, IL-6, and TNF [6].

According to the origin concentration of IL-1, the synaptic plasticity that underlies learning and memory in the nervous system of adults has been suggested to be modulated, with effects that can be either boosting or inhibiting. Interleukin-1 (IL-1) is a proinflammatory cytokine that functions as an agonist at the interleukin-1 receptor. Its gene is found on chromosome 2q13. The genetic variation in IL-1, specifically the -511 C/T (rs16944) mutation, may enhance the risk of schizophrenia, according to several association studies in Caucasian groups [7]. Meanwhile, Japanese studies showed that IL-1β -511C/T polymorphism may be a factor in schizophrenia [8].

Studies using pro-inflammatory cytokines have been conducted in North Sumatra, such as Amin et al. in 2019, with the title tumor necrosis factor-α levels and their relationship with cognitive function in schizophrenia within Malayan-Mongoloid tribe [3]. Therefore, this study aimed to determine the relationship between the IL-1β -511C/T polymorphism and Bataknese with schizophrenia.

2 Patients and Methods

2.1 Patients and Study Design

This study, which employed a cross-sectional methodology, was carried out for 4 months in 2021 at the North Sumatra Mental Hospital's Inpatient Installation (R. S. J. Provsu) Prof. M. Ildrem. The participating patients were selected through inclusion and exclusion criteria. Inclusion criteria included ODS Batak tribe diagnosed based on DSM-1V (PPDGJ-III-in Indonesia), Age 18–45 years, Two generations of first-degree family, and were Batak tribe. Meanwhile, the exclusion criteria were consuming alcohol and other addictive substances (except nicotine and caffeine) as well as having a history of neurological diseases, endocrine problems, autoimmune diseases, and prior psychiatric disorders. The number of samples used was 120 ODS (27 women and 93 men) and 120 healthy control (49 women and 71 men).

2.2 Methods

To determine the polymorphism we used PCR-RFLP and Ava 1 restriction enzyme is used to digest specific fragment of the -511 IL-1 β. Primers were obtained from previous studies and blasted to confirm the results. The genotyping and DNA isolation was performed at the integrated laboratory of the Faculty of Medicine, University of North Sumatra. Blood sampling on the subject was carried out in the amount of 7 ml from the anterior cubital vein. In order to isolate DNA using the salting out method, the blood was placed into a vacutainer containing ethylenediamine tetraacetic acid (EDTA) and kept at 4 to −80 C.

Furthermore, genomic DNA was extracted from the sample subjected to freezing using standard methods. The single base variant at position -511 in the IL-1β promoter region was read by PCR using the method by Wilson et al., in 1992, oligonucleotide primers (forward) 5'TGGCATTGATCTGGTTCATC3' and (reverse) 5'GTTTAGGAATCTTCCCACTT3'.

Denaturation at 94 °C for 5 min, then 30 cycles of 94 °C for 30 s, 55 °C for 30 s, and final extension at 72 °C for 7 min made up the PCR cycle conditions. The PCR products were stored at 37 °C for 1 night with 10 units of Ava 1 restriction enzyme for IL-1β.

2.3 Statistical Analysis

Initial normality test by using the Kolmogorov-Smirnov normality test was used for numerical data (age, onset, length of illness, and PANSS score). All numerical data were not normally distributed, thus median (min-max) was used to present the data. Allelic and genotypic frequency were compared by using Chi Square and logistic regression respectively.

2.4 Results

Men dominated more than women, namely 93 (77.5%) in the ODS and 71 (59.2%) in the control group. Furthermore, the median age was 36 and 29 years for the ODS and the control group, while the median disease onset was 25 years, with 10 years of median length of illness in ODS. The PANSS score in the ODS group was 97 (Table 1).

The frequency of C and T allele occurrences in the ODS group was 61.6% and 38.4%, respectively, while in the control was 45.8% and 54.2%. Chi-square analysis showed a p-value = 0.001, meaning that there was a significant difference between the frequency of allele occurrences in the ODS and control groups. The OR obtained was 1.901 with an IC of 1.322–2.735 (Table 2).

The frequency of CC, CT, and TT genotype occurrences in the ODS group was 40%, 43.3%, and 16.7%, respectively, while in the control was 19.2%, 53.3%, and 27.5%. Based on the logistic regression analysis results, the chi-square value for the genotype (CC vs TT) was p = 0.019 with OR = 0.414 and CI 0.198–0.866, while for (CT vs TT) was p = 0.388 with OR = 0.746 and CI 0.384–1.451 (Table 3).

Table 1. Demographic characteristics of Batak ODS and healthy control

	Patient (n = 120)	Control (n = 120)	*P-value*
Gender			
Male	93 (77.5)	71 (59.2)	
Female	27 (22.5)	49 (40.8)	0.004*
Age (Years)	36 (24–44)	29 (20–44)	<0.001**
Onset	25 (21–34)		
Lenght of illness	10 (1–20)		
Total Panss Score	97.50 (81–120)		
** Chi-square with continuity correction** Mann-Whitney U*			

Table 2. Comparison between IL-1β -511 C/T variant polymorphisms in the ODS and control groups of Batak Tribe obtained by the chi-square procedure

Allele	Patient (n = 120)	Control (n = 120)	*P-value*	OR (95% CI)
C	148 (61.6)	110 (45.8)	0,001	1.901 (1.322–2.735)
T	92 (38.4)	130 (54.2)		

Table 3. Comparison between genotype polymorphisms of the IL-1β-511 C/T gene in Batak Tribe ODS and control obtained by logistic regression procedures.

Genotype	Patient (n = 120)	Control (n = 120)	P-value	OR (95% CI)
CC	48 (40)	23 (19.2)	0.019	0.414 (0.198–0.866)
CT	52 (43.3)	64 (53.3)	0.388	0.746 (0.384–1.451)
TT	20 (16,7)	33 (27.5)	Comparison	

3 Discussion

In this present study, vast majority of Bataknese with schizophrenia was male. This is consistent with a study analyzing the trends in incidence and DALYs in schizophrenia globally. This study showed a difference between men and women. In 2017, men were around 6.51 million cases while women were 6.14 million, and the highest incidence rate was found in age 20–29 and 30–54 years [9].

The median onset of illness in the ODS group is 25 years with a minimum and maximum of 21 and 34 years. The median length of illness is 10 years with a minimum and maximum of 1 and 20 years. At the onset, no specific age is associated with schizophrenia where this disorder begins with a prodromal stage. The most common early onset is the age of 15–30 years and a chronic disease that disrupts patients and their families with a major social and economic impact [10].

The results showed that there is a significant difference in the IL-1β -511 C/T polymorphism, hence, it can be a risk factor for schizophrenia in Bataknese. This is consistent with a study in Italy that investigated the relationship between gene polymerism of IL-1β -511 C/T and IL-1RA in ODS. This study involved 346 subjects consisting of 169 ODS and 177 controls, and the results showed that the C allele proportion was significantly more frequent than in the control group. This is in line with a study in Japan, where the C allele proportion was significantly more frequent in the ODS group than in healthy control with an OR of 1.22, a CI of 1.05–1.41, and a p-value of 0.0089 [8, 11]. However, this is different from the study in Finish, where there was no difference in allele frequencies between the two groups [12].

The genotype of the IL-1β -511 C/T polymorphism does not have a significant relationship with the incidence of schizophrenia. These results are in line with Sasayama et al.in 2011, which conducted a study of the same gene. The subjects were Japanese individuals with no biological relationship based on self-reports. Furthermore, they were recruited from the outpatient clinic of the National Center of Neurology and Psychiatry Hospital, Tokyo, Japan [8].

4 Conclusions

The results showed that the IL-1β-551 C/T polymorphism has a relationship with the incidence of schizophrenia. Therefore, the IL-1β -511 C/T polymorphism may be a risk factor for schizophrenia in Bataknese.

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Ethics Approval and Consent to Participate. This study was approved by the Research Ethics Committee at the Faculty of Medicine, the University of North Sumatra, with the letter number 814/KEP/USU/2021 on August 31, 2021. All participants have written and signed consent to participate.

Transparency Declaration. Competing interests: None to declare.

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