

Research Article

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Relationship between Duration of Illness and Onset with PANSS and Interleukin-6 in Schizophrenia

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Abstract

Background: Schizophrenia is a severe mental disorder characterized by disturbances in mind, perception and behaviour. Studies of inflammatory response activity in schizophrenia have aberrant cytokines, especially proinflammatory cytokines interleukin (IL)-6. This study uses an observational analytic study, with a sample of 60 male patients.

Aim: The aim of the study was to determine the relationship duration of illness, age of onset with Positive and Negative Syndrome Scale (PANSS) and Interleukin-6 (IL-6).

Result: Pearson correlation test: the duration of sickness correlation with PANSS shows that there is a Very strong Relationship and a moderate positive direction (p<0.005, r=0.476), the long correlation of pain with IL-6 shows that there is a very strong and positive direction (p<0.005, r=0.670); correlation between onset with PANSS shows that there is a very strong relationship and a moderate positive direction (p<0.005, r=0.670); correlation between onset with PANSS shows that there is a very strong relationship and a moderate positive direction (p<0.005, r=0.539), the onset age correlation with IL-6 showed no relationship with negative direction (p>0.005, r=0.370); relapse frequency correlation with PANSS) showed no relationship and weak positive direction (p>0.005, r=0.201).

Conclusion: There was a significant relationship between duration of illness, age of onset with total PANSS. There was a relationship among duration of illness, age of onset with IL-6.

Keywords: Duration of illness; Onset; Interleukin-6; PANSS

Introduction

Schizophrenia is a severe mental disorder indicated by disturbances in mind, perception and behavior [1]. Approximately 1%-2% of the world population suffers from schizophrenia in their lifetime. Thereabouts 2.5 million or 1% of Indonesians suffer from mental disorders which has not been yet derived a conclusion about these exact causes. Based on survey results, the incidence of mental disorder in Indonesia is estimated to be 0.2%-0.8% a year [2]. Men tend to suffer from schizophrenia a little earlier than women, the peak age of onset in men is 15-25 years, while women are 25-35 years. The onset of schizophrenia before the age of 10 or after the age of 50 years is very rare. Approximately 90% of patients in the treatment of schizophrenia are between the ages of 15 and 55 years. The incidence of schizophrenia in men is slightly greater than in women. The incidence in women is higher after the age of 30 years. The average age of onset is 18 in men and 25 years in women [3].

The accurate cause of schizophrenia is still unknown, but the dopamine hypothesis is the most developed hypothesis among others and becomes the basis of many rational drug therapies [4]. In schizophrenia, extracellular dopamine is increased. These dopamine levels play an important role in changing different feelings and moods. If dopamine levels are unbalanced, excessive or deficient, patients can experience positive symptoms and negative symptoms. Reduced dopamine in the mesocortical pathway can cause negative symptoms

and cognitive impairment. When dopamine increases in the mesolimbic pathway, it can cause positive symptoms of schizophrenia [5]. Clinical examinations that describe the psychopathological condition of patients are based on changes in Positive and Negative Syndrome Scale (PANSS) scores. PANSS is used to measure the success of treatment [6].

Research on dopamine as the main cause of schizophrenia has not revealed the mechanism of schizophrenia as a whole, so other research needs to be done in an effort to explain the mechanism. Recent studies of inflammatory response activity in schizophrenia have aberrant cytokines, especially proinflammatory cytokines interleukin (IL)-6 in peripheral blood or cerebrospinal fluid in schizophrenic patients. Data from 62 studies involving a total sample of 2298 schizophrenic patients and 1,858 healthy volunteers, showed an increase in IL-6 in schizophrenic patients [7]. This study aimed to determine the relationship of age, duration of illness, age of onset, frequency of relapse with PANSS and IL-6.

Materials and Methods

This research was performed under approval of the ethics committee of Faculty of Public Health, Airlangga University Indonesia. This research used analytic observational study and was conducted from October 2017 to March 2018 at Mental Hospital Dr. Radjiman Wediodiningrat Lawang Malang. The inclusion criteria of respondents were male patients diagnosed with schizophrenia, aged between 18-50 years. Exclusion criteria were physical/physical disabilities, organic

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mental disorders and ECT indications. Demographic characteristics (age and sex), marital status, education level, occupation, onset age, duration of illness were taken from the interview results. PANSS examination was carried out by psychiatrists from the mental hospital of Dr. Radjiman Wediodiningrat Lawang.

Ingredients of the IL-6 Kit for IL-6 include standard solution (640 ng/L) 0.5 ml, Pre-coated ELISA Plate, Standard diluent 3 m, streptavidin-HRP 6 ml, stop solution 6 m, Substrate Solution A 6 ml. solution B substrate 6 ml, 20 ml wash buffer concentrate (30x), biotin-conjugate anti-human IL-6 antibody 1 ml, plate sealer and zipper bag. The ingredients was examined in the Laboratory of Physiology, the University of Brawijaya Malang.

Statistic Analysis

Categorical variables are expressed as frequencies and percentages. Continuous variables are explained by mean and standard deviation. Statistical analysis was performed using the statistics of IBM SPSS for windows version 22.0 (IBM Corp, Armonk, NY, USA). p<0.05 was considered statistically significant.

Results

There were 60 patients. 100% of patients were male with average age between 31-50 years (83.2%). Most of them were unmarried (70%), with education level of primary school (35%) and junior high school (35%). Most of them were unemployed (85%) with average age ranging from 26-35 years (50%), the duration of illness was mostly 11-20 years (53.4%). A complete description of the characteristics of the respondents is explained in Table 1 and Table 2. Most of medical

Characteristics of respondents	Characteristics of respondents Category		%	x ± SD	р
Age	21-30 year	8	13	38,7 ± 7,12	0.005
	31-40 year	27	45		
	41-50 year	25	42		
Sex	Male	60	100.9		
	Unmarried	42	70		0,837
	Married	7	11,7		
	Divorced	11	18,3		
Education	Never attending school	5	6,7	0,54	
	Primary School	20	35		
	Junior high School	21	35		
	Senior high School	14	23.3		
Employment	Unemployed	51	85		0,862
	Employed	9	15		

diagnoses were Hebefrenic schizophrenia (80%) which is displayed in Table 3. Meanwhile, the results of PANSS and IL-6 examinations are explained in Table 4.

Table 1: Characteristics of respondents.

Characteristic of respondents	Category	n	%	x ± SD
Onset	<20 years	14	23,3	26,38 ± 6,4
	21-30 years	28	46,7	
	31-40 years	16	26,7	
	>40 years	2	3,3	
Duration of illness	≤ 5 years	5	8,3	11,5 ± 4,55
	6-10 year	23	38,3	
	11-20 year	32	53,4	

 Table 2: History of illness respondents.

Characteristic of respondents	Category	n	%
Medical diagnosis	Hebephrenic	48	80
	catatonic	1	2
	Undifferentiated	1	2
	Simplex	10	16

Table 3: Medical diagnosis of respondents.

Characteristics of respondents Category x ± SD

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PANSS	Negative Symptoms	30,83 ± 9,40
	Positive Symptoms	9,11 ± 6,11
	General Symptoms	36,55 ± 14,03
	Total	76,50 ± 22,83
IL 6		119,67 ± 78,65

Table 4: PANSS.

In Table 5, Pearson correlation test the duration of illness and PANSS produced the highest probability of total PANSS of 0,000, so there was a very significant relationship between the duration of illness and total PANSS. The correlation coefficient of duration of illness with total PANSS is 0.476. This shows a positive (directed) and moderate relationship.

Category		PANSS			IL-6	
		Negative symptoms	Positive symptoms	General symptoms	Total	
Duration of illness	r	-0,174	0,148	-0,105	0,476	0,67
	р	0,43	0,26	0,424	0,000	0,000
	r	0,276	-0,097	0,020	0,539	-0,37
	р	0,031	0,461	0,880	0,000	0,004

Table 5: Correlation results of several variables.

The relationship between the age of onset and PANSS produces the highest probability of total PANSS of 0.539, indicating a direct and positive relationship between the age of onset and total PANSS with correlation coefficient (r) of 0.000. The correlation coefficient between the duration of illness with IL-6 is of 0.000, therefore the relationship was very significant. So there is a very significant relationship between the duration of illness and IL-6. Meanwhile the duration of illness with IL-6 of 0.67 indicates a positive (direct) and strong relationship. The probability level of onset age with IL 6 levels is of 0.004, indicating no significant relationship between the onset of age with IL 6; the correlation coefficient of the relationship is -0.37, referring to negative relationship.

Discussion

Sociodemography of schizophrenia

The age of respondents reflects personal life experience with age ranging from 31-40 years (45%) and 41-50 years (42%). The results of this study do not support the previous theory, stating that patients with age of 25-35 are likely to suffer from schizophrenia 1.8 times more than those of 17-24 years [7]. Hurlock explains that early adulthood is a period of self-adjustment to new lifestyle once they gain freedom [8]. The age of adolescents and young adults are indeed at high risk, entering new stage of life with full of stressors. This period makes youth very susceptible to the emergence of various kinds of disorders that have an impact especially on their psychological health [9]. Those affected with schizophrenia will experience dramatic decline of social function. A study conducted in six European countries found that more than 80% of adult schizophrenic patients experience persistent social functioning problems [10]. The disruption of social function is

an important and fundamental factor that causes schizophrenic patients who are unable to adjust to the daily life.

The marital status of respondents was used to inform researchers about psychosocial factors that might affect their mental disorders i.e., marital problems, interpersonal relationship problems, family factors and other psychosocial factors (physical illness, victims of natural disasters and accidents, legal problems, rape and so forth) [11]. The results of interview show that average numbers of respondents are unmarried. The research data supports the existing theory that unmarried person is more likely to suffer schizophrenia than those of married person; because marriage is required for ego exchange and spouse behaviour identification toward harmony [7]. In fact, attention and compassion from beloved ones are important to gain satisfying life. The education level of respondents is also used to provide information about the effect of education on mental disorder. The result of interview found that average number of respondents was elementary and junior high school.

This research data supports the previous theory that low education induces stress, resulting in mental disorders [12]. The research data is also in line with the opinion of Friedman [13] saying that people who have a higher level of education already have more knowledge to deal with health issues, which subsequently better at solving a problem. In other words, those with low education are less able to solve problem or make decisions. Knowledge and cognitive domain is very important to influence someone's behaviour. Thus, knowledge can affect human behaviour in maintaining and improving their mental health.

Employment is identified to be a factor of stress that could lead to schizophrenia [11]. The results of interviews suggest that average number of respondents is unemployed. This goes in line with the results of the study by Mallet, et al. [14], there was a significant relationship between employment status and the onset of schizophrenia. Unemployed people will be more easily stressed because of high level of stress hormone (Catecholamines level) and feeling of worthless. Employment allows people to have a sense of optimism about future and have more enthusiasm than unemployed people. Unemployed people are often regarded as those with no interest of social life; they have no earnings, few of friends or acquaintes, no social status, job, performance, activities, status and low self-esteem.

The age of onset was used to identify age of respondents initially experience the schizophrenia. The age of onset was mostly between 26-33 years. The data of this study did not support the existing data of American Psychiatric Association (APA) in 1995 [15], which stated that the age of onset of 75% of people with schizophrenia was between 16-25 years. Based on the study of the age of onset with cognition in schizophrenia, the earlier the onset age, the higher decrease in IQ, psychomotoric abilities and verbal memory. The duration of illness is used to determine the range of illness from initial stage of being declared a mental disorder (Schizophrenia) until the study was conducted. The duration of illness of schizophrenia was mostly between 11-20 years (53,4%). The result of the study supported data from WHO that most of the duraction of illness is more than 10 years.

According to WHO, the length of care for schizophrenic patients consists of: 14% for approximately 1 year, 12% for 1-4 years, 25% for 5-10 years, and 49% for more than 10 years. The duration of the respondent's illness reflects the chronicity of the disease suffered by the patient. The longer duration of illness, the longer the treatment process is. The saturation effect in taking medication, leads to drop out of medication as they feel healthy which result s in the relapse rate of schizophrenics. The frequency of relapse was used to identify some symptoms identical to its previous one, which subsequently bring the students to be hospitalized again. 100% of respondents experience relapse with a frequency of relapse from 7-10 times. This result was not in line with a previously published article in the journal of BMC psychiatry in 2013, stating that 80%-90% schizophrenic symptoms experience relapse. In addition, the data did not support the prognosis for schizophrenia, stating that approximately 50% of schizophrenic patients suffer periodic relapse [16].

The rate of relapse is related to the duration of illness and the course of illness. Schizophrenic patients experience chronic mental disorders with varying course of illness. In addition, schizophrenic patients experience reality disorders and inability to make decisions. In hospitals, health workers, especially doctors and nurses, are responsible for monitoring drug administration and patient care, at home the work of health workers is replaced by the family. The role of the family is very influential in monitoring drug administration and care of patients at home.

Medical Diagnosis

Medical diagnosis is identification of disease type based on signs and symptoms using the PPDGJ III guidelines. 80% of medical diagnoses from respondents were hebefrenic schizophrenia, schizophrenia simplex as of 16.75%, catatonic schizophrenia and undefined schizophrenia up to 1.75%. Each schizophrenic falls under a subtype of schizophrenia defined by a unique indicator. This indicator may be one dominant symptom only or a combination of positive and negative symptoms [17]. The kinds of symptoms that are utilized to make a diagnosis of schizophrenia differ between affected people and may change from one year to the next within the same person as the disease progresses. Different subtypes of schizophrenia are defined according to the most significant and predominant characteristics present in each person at each point in time. The result is that one person may be diagnosed with different subtypes over the course of his illness.

PANSS

Assessment of symptoms of schizophrenia uses the Positive and Negative Syndrome Scale (PANSS) indicators [18]. Positive and Negative Syndrome Scale is a valid measurement tool to assess the severity of symptoms experienced by schizophrenic patients and to assess the therapeutic output. PANSS assessment on respondents: mean and deviation standard of negative symptoms (30.83 ± 9.40), positive symptoms (9.11 ± 6.11), general symptoms (36.55 ± 14.03), total PANSS assessment ($76,50 \pm 22.83$). PANSS has 30 points of assessment with 3 scales (positive scale=7 points; negative scale=7 points; general psychopathology scale=16 items). The relationship between duration of illness and age onset PANSS showed that there was no relationship between each negative symptom, positive symptoms and general symptoms in schizophrenic patients.

Schizophrenia is caused by complex factors, namely genetic, developmental and environmental factors. Positive symptoms can be controlled in most patients with currently available antipsychotics. Instead, they are less effective against neurocognitive dysfunction, deficits in social cognition and negative symptoms, which greatly contribute to poorly functional outcomes. Social cognition disorders have a large impact on functional outcomes and can trigger other symptoms. This study comes with some limitation as for the relevancy of negative symptoms toward the functional outcomes is not extensively discussed. Therefore, further research should be taken with the inclusion of functional outcomes in schizophrenia in order to provide more established framework of theory particularly in developing countries.

Interleukin 6 (IL-6)

In distress conditions, functional changes occured in the form of hormonal changes and neurotransmission, including increased noradrenergic activity and cortisol levels. If it became chronic, it would result in structural changes, in the form of atrophy of pyramidal cells and decreased hippocampal volume, and increased activity of the Hypothalamo-Ititariadrenal Axis (HPA axis) resulting in changes in levels of Interleukin-6 (IL-6). The results showed that there was a relationship between duration of treatment and age of onset with IL-6. This is in line with previous studies that IL-6 was associated with long illness and onset age [19-21]. In schizophrenia, age, the age of onset/ disease onset are important factors of clinical outcome [22]. Earlier age of onset correlates with worse disease prognosis and increased symptom presentation [23,24]. This finding provides importantly supporting information for the pathophysiological role of inflammation in schizophrenic patients [25,26]. These results imply that, at least in young people with comparatively low levels of chronic inflammation, social conflict creates a potential for hyperinflammatory responses that requires an exogenous immunological stimulus for realization [27-29].

Conclusion

There is a relationship between duration of illness, age of onset with total PANSS. There is a relationship, especially long illness, age onset with IL-6.

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