OBESITY AND PSYCHO-PATHOLOGICAL SYMPTOMS AND PSYCHOSOCIAL RELATIONSHIP WITH ANTI PSYCHOTICS AND DISC1 GENE AS GENETIC MARKER OF SCHIZOPHRENIA SUSCEPTIBILITY

BY

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ABSTRACT

Schizophrenia is a chronic debilitating mental disorder with a lifetime risk estimated at about 1%, regardless of ethnicity. The ideal outcome of schizophrenia treatment is to improve psycho-social function and quality of life thus limiting the debilitating condition. This can be achieved by reducing the devastating effects of its psycho-pathological symptoms. Unfortunately, the introduction of atypical anti-psychotic drugs is linked to obesity, an issue of concern as it is a co-morbid condition that is closely related to metabolic syndrome. Additionally, there are substantial evidences that suggest Disrupted-in-Schizophrenia-1 gene (DISC1) function in neurodevelopment. This supported DISC1 locus as candidate gene of schizophrenia and a potential target for treatment of schizophrenia. The current research encompasses three different sub-studies. Firstly, the study investigated the relationship between psycho symptoms and psycho-social function and anti-psychotics in the prediction of psycho-social function among schizophrenia patients. Secondly, the study assessed the correlation of body mass index with antipsychotics. Subsequently, the data was compared with Malaysian Adult Nutrition Survey (MANS). Finally, the study assessed the association of DISC1 gene as genetic susceptibility marker of schizophrenia. A total of 240 schizophrenia patients and 350 control healthy individuals participated in the study. A cross sectional approach was adopted for the first and second study and unmatched case-control for the third study. Methods used include interview, psychiatric scales assessment and genotyping for DISC1 markers. There was an inverse relationship between psycho-symptoms and psychosocial functions. Disorganization (DIS) was the only significant predictor to all dimensions of psycho-social functions. Typical anti-psychotics significantly predicted social function negatively as compared to Sulpiride *($b=-0.152$, $p=0.028$)*.Obesity was 2-fold greater than the reference population. Body mass index was generally related to antipsychotic drugs *($\chi^2 = 33.42; p = 0.04$)*.Finally, the study found two SNPs, rs4658971 and rs1538971 within DISC1 gene that predisposed to schizophrenia andrs2509382located in chromosome 11 that was associated with schizophrenia in males. The study concluded four important findings. Firstly, obesity was common among schizophrenia patients and this could be attributed to anti-psychotics. Secondly, DIS as predictor to all social dimensions emphasized the importance of cognition in schizophrenia. Thirdly, Sulpiride predicted better social function than typical antipsychotics. Lastly, the study provided significant evidence of DISC1 gene as marker of schizophrenia susceptibility.

خلاصة البحث

مرض انفصام الشخصية هو من الامراض النفسية المزمنة والموهنة والتي تشكل خطرا دائميا بالاصابة بالمرض لحوالي 1% من الاشخاص مهما يكن نوع اجناسهم.ان الهدف المثالي لعلاج مرض انفصام الشخصية هو تحسين الوظائف النفسية الاجتماعية وتحسين نوعية الحياة وبهذا تقلل حالة الوهن والضعف وهذا يمكن الحصول عليه وذلك بتقليل التاثيرات المدمرة للاعراض النفسية والمرضية.ان ظهور ادوية الامراض النفسية الغير قياسي فانه مرتبط ومع الاسف بداء السمنة وهذا يشكل مضاعفات اضافية مرتبطة بشدة مع متلازمة الايض.بالاضافة الى ذلك, هنالك دلائل توضح اعتلال في عمل جين انفصام الشخصية رقم 1خلال تطور الجهاز العصبي وذلك يدعم موقع الجين المسؤول عن انفصام الشخصية مما يجعله هدف لعلاج المرض.هذا البحث الجاري يحتوي على ثلاثة محاور مختلفة:اولا: الدراسة تحتوي على العلاقة مابين الامراض النفسية والوظائف الاجتماعية النفسية مع ادوية الحالات النفسية مما يساعد على توقع الوظائف النفسية الاجتماعية بين مرضى انفصام الشخصية.ثانيا: هذه الدراسة او البحث تخمن العلاقة بين مؤشر كتلة الجسم مع ادوية الامراض النفسية وبالتالي فان المعلومات قورنت بالمسح الغذائي الماليزي للبالغين.واخيرا فان هذه الدراسة تربط العلاقة بين اعتلال جين انفصام الشخصية رقم 1 مع مؤشر القابلية الجينية للاعتلال لمرض انفصام الشخصية.لقد شارك 240 مريض مصاب بانفصام الشخصية مع 350 شخص سليم كمجموعة سيطرة في هذا البحث ولقد تم استخدام دراسة مقطعية عرضية للدراستين الاولى والثانية وتم استخدام الحالات المسيطر عليهاغير المطابقة بالنسبة للدراسة الثالثة وان الطرق المستخدمة احتوت على مقابلة, مقياس تقييم نفسي, ودراسة جينية لمؤشرات اعتلال جين انفصام الشخصية رقم 1.وجدت علاقة عكسية مابين الاعراض النفسية والوظائف النفسية الاجتماعية. وان عدم التنظيم كان المؤشر الوحيد ذو اهمية في كل الاتجهات للوظائف النفسية الاجتماعية.استخدام الادوية النفسية المثالية اظهرت بشكل واضح وظائف اجتماعية بصورة سلبية بالمقارنة مع السلبرايد (ب= 0.028 بي =0.152)السمنة كانت اكثر بضعفين من المصدر البشري وان مؤشر كتلة الجسم كان له علاقة عامة بالادوية النفسية(”× =33.42 ب =0.054)اخيرا وجدت الدراسة 2اس ان بي اس,4658971ار اس و1538971ار اس ضمن جين اعتلال انفصام الشخصية رقم 1 والذي ادى الى مرض انفصام الشخصية و 2509382ار اس الموجود في الكروموسوم الحادي عشر والمرتبط بمرض انفصام الشخصية في الرجال.الدراسة استنتجت اربعة حقائق مهمة:اولا: داء السمنة موجود بكثرة بين مرضى انفصام الشخصية وهذا قد ينسب الى استخدام ادوية الامراض النفسية.ثانيا: عدم التنظيم كمخمن لكل الاتجاهات الاجتماعية يوضح اهمية الادراك في انفصام الشخصية.ثالثا: دواء السلبرايد يعطي دلالة احسن للوظائف الاجتماعية عن الادوية النفسية المثالية.اخيرا: الدراسة اعطت ادلة مهمة لاعتلال جين انفصام الشخصية رقم 1 كمؤشر لقابلية الاصابة بانفصام الشخصية.

APPROVAL PAGE

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DECLARATION

I hereby declare that this thesis is the result of my own investigation, except where otherwise stated. I also declare that it has not been previously or concurrently submitted as a whole for any other degrees at IIUM or other institutions.

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LIST OF ABBREVIATIONS

µL	Microlitre
µM	Micromolar
AKTI	V-akt Murine Thymoma Viral Oncogene Homolog-1
BMI	Body mass index
CI	Confidence interval
CNV	Copy number variants
COMT	Catechol-O-Methyltransferase
DAOA	D-amino-acid oxidase activator
DIS	Disorganization
DISC1	Disrupted in schizophrenia 1
DNA	Double stranded Nucleic Acid
DTNBPI	Dysbindin
EDTA	Ethylenediaminetetraacetic Acid
EMO	Emotion
EXC	Excitement
fRFLP	Forced restriction fragment polymorphism
GAF	Global assessment of functioning scale.
GWAS	Genome Wide Association Scan
HTAA	Hospital TengkuAmpuanAfzan, Kuantan.
HWE	Hardy Weinberg Equilibrium
ICD	International classification of disease
LD	Linkage disequilibrium
MAF	Minor allele frequency
MANS	Malaysian Adult Nutrition Survey
$MgCl_2$	Magnesium chloride
mL	Mililitre
mM	Milimolar
NEG	Negative
NRG1	Neuregulin 1
OR	Odds ratio
PANSS	Positive and Negative syndrome scale
PCR	Polymerase chain reaction
POS	Positive
PPP3CC	Protein phosphatase-3 Catalytic Subunit Calcineurin Isoform
PSP	Psychosocial and performance scale
RFLP	Restriction fragments length polymorphism
RFLP	Restriction fragment polymorphism
RGS1	Regulator of G-protein Signaling 4
SNP	Single nucleotide polymorphism
SOFAS	Social and occupational functioning assessment scale
TBE	Tris Boric EDTA
WHO	World Health Organisation
µL	Microlitre

μM	Micromolar
AKTI	V-akt Murine Thymoma Viral Oncogene Homolog-1
BMI	Body mass index
CI	Confidence interval

CHAPTER ONE

INTRODUCTION AND LITERATURE REVIEW

1.1 INTRODUCTION

Schizophrenia is a psychotic disorder, the causes of which are still largely unknown. It involves a complex set of disturbances of thinking, perception, affect and social behaviour. No society or culture is free from schizophrenia (Jablensky, 2000). This illness is a serious public health problem (Colton & Manderscheid, 2006; Jablensky, 2000; Jones, Macias, Barreira, Fisher, Hargreaves, & Harding, 2004). There is no specific cause of Schizophrenia (National Institute of Mental Health, United States, 2009). The disease is considered a complex disease with an estimated heritability at up to 80% (McGuffin, Owen, & Gottesman, 2002). Evidence suggesting the role of genetics in schizophrenia is mainly derived from twins and adoption studies. Schizophrenia traits among monozygotic twins who theoretically share 100% sequence similarity was around 40-75% (Folstein, 1996; Franzek & Beckmann, 1998). The incidence was much lower at around 4%-15% among dizygotic twins who theoretically share 50% sequence similarity (Cardno, Marshall, Coid, Macdonald, Ribchester, Davies, Venturi, Jones, Lewis, Sham, Gottesman, Farmer, McGuffin, Reveley, & Murray, 1999; Onstad, Skre, Torgersen, & Kringlen, 1991).

It is postulated that many genes contribute to Schizophrenia susceptibility. It has been hypothesized that the combination of susceptible genes and environmental stressor lead to disruption of several hypothetical pathways implicated in Schizophrenia (Lang, Puls, Muller, Strutz-Seebohm, & Gallinat, 2007). On the basis of strong familial predisposition to schizophrenia, searching for genetic entities that

contribute to the susceptibility to schizophrenia is sensible. Efforts have been made by many studies to identify the candidate genes for schizophrenia. As any other complex diseases, genetic variability are believed to be responsible to individual susceptibility to the disease. Among the many candidate genes studied, theDisrupted-in-Schizophrenia-1 gene (DISC1) locus has remained a gene that has shown encouraging positive association (Hennah, Tuulio-Henriksson, Paunio, Ekelund, Varilo, Partonen, Cannon, Lonnqvist, & Peltonen, 2005; Qu, Tang, Yue, Ruan, Lu, Liu, Zhang, Han, Zhang, Wang, & Zhang, 2007).

However, many studies reported conflicting associations between DISC1 gene and schizophrenia. This warrants further work that is it applies to specific populations. Review on the functional studies of DISC1 revealed diverse role of DISC1in neurodevelopment, cytoskeletal function and cAMP signaling (Chubb, Bradshaw, Soares, Porteous, & Millar, 2008). Several genes that interact with DISC1 have also been defined as independent genetic susceptibility factors for psychiatric illness (Chubb et al., 2008). The sites for targeting therapy aiming towards DISC-1 related pathology werealso recently discussed (Hikida, Gamo, & Sawa, 2012). Therefore, the DISC1 gene markers for schizophrenia susceptibility relevant to local population should be identified and clarified. This might be helpful in future, in making stand or opinion on therapy targeting to this gene and its products.

With regards to the management of schizophrenia, the progress of pharmacotherapy in the last 50 years has been well documented. The assessment of the effectiveness of antipsychotic has changed in parallel to the introduction of newer anti-psychotics. With the introduction of antipsychotic in the late1950's, the management aim of schizophrenia has significantly changed. At that time, the aim was rather simple which was to control aggression, self-harm and to enable better personal

hygiene. Further inventions of newer antipsychotic drugs, refinement of the drugs delivery system and optimization of therapy have altered the treatment goals to more specific objectives such as a reduction of certain psycho-pathological symptoms and side effects control of the drugs. In chronic debilitating diseases such as schizophrenia, the ideal outcome of treatment is to improve psycho-social function and quality of life of the patients. This can be done by reducing the devastating effects of psycho-pathological symptoms. The earlier treatment that emphasized on treating the negative symptoms for improvement of quality of life in schizophrenia is not completely fruitful. It became clear that additional symptoms of schizophrenia such as depressive and cognitive deficits significantly influence the psycho-social function and quality of life of schizophrenia patients (Lysaker & Davis, 2004). Recovery from schizophrenia is considered successful once the patient is accepted by the community, and is socially and financially independent. Understanding the basic relationship between psycho-pathological symptoms and psychosocial performance as well as the effect of anti-psychotics on psycho-social performance, could bring tremendous advantage in the management of schizophrenia.

Among the most discussed side effects of the second generation anti-psychotics are obesity and development of metabolic syndrome. The link between antipsychotics, schizophrenia and obesity is not something that is entirely new or suddenly appeared after the introduction of second generation anti-psychotics. Earlier reports before 1960 had suggested that chlorpromazine and reserpine were strongly associated with obesity. Subsequently, the second-generation antipsychotic drugs have also been associated with the likelihood of gaining weight (Allison, Mentore, Heo, Chandler, Cappelleri, Infante, & Weiden, 1999; Goudie, Cooper, & Halford, 2005). Conflicting to this notion however, it was noted that although themean body mass

index (BMI) was significantly higher among schizophrenia patients than non-schizophrenia participants between the year 1987 and 1996, the incremental trend of the BMI index was not specific to the atypical antipsychotic drugs introduced at that time (Homel, Casey, & Allison, 2002). Investigations on the prevalence of obesity among our own schizophrenia patients may give a clearer picture on the severity of the condition (obesity) within the local context. Furthermore, the relationship between obesity and the antipsychotics used can be determined. The findings may help in the current and future management of schizophrenia.

1.2 SCHIZOPHRENIA

1.2.1 Epidemiology and Burden of Disease

The prevalence of schizophrenia varies in different populations. It is reportedly as high as 7 in 1000 population in the United States to as low as 1.4 in 1000 population in some parts of Indonesia (Jablensky, 2000). The lifetime risk of having this disabling chronic mental disorder is estimated at about 1%, regardless of ethnicity. Schizophrenia often begins in early adulthood, affecting men more than women. The relative risk for males compared to females is 1.42 (95% CI: 1.31-1.51) (Aleman, Kahn, & Selten, 2003). In Malaysia, the National Mental Health registry has 7351 notified cases of Schizophrenia between the year 2003 and 2005 in which 3714 were new cases. Among the 7351 cases notified, two third were within the reproductive age (20– 40 years old), 70% of them were unemployed and males constituted 62% of the cases(Aziz, Salina, Abdul Kadir, Badiah, Cheah, Nor Hayati, Ruzanna, Sharifah Suziah, & Chee, 2008).

Globally, schizophrenia with other neuropsychiatric illnesses accounted to almost one third of the cases of Years Lost due to Disability in adults aged 15 years

and above [World Health Organisation (WHO), 2004]. The overall health care cost for Schizophrenia in the United States in 2002 was estimated to be USD 62.7 billion (Wu, Birnbaum, Shi, Ball, Kessler, Moulis, & Aggarwal, 2005).In Malaysia, there is no specific data on the health care cost for Schizophrenia. However, we assume by combining the health care cost with the loss of productivity due to unemployment, the cost for Schizophrenia in Malaysia could also reach billions of ringgit.

1.2.2 Etiology of Schizophrenia

Epidemiological research from the last century has identified a set of risk factors for schizophrenia. The risks are categorized as prenatal and antenatal risk factors (R. Murray, Jones, Suser, Os, & Cannon, 2003). Having a first-degree family history of schizophrenia is associated with an odds ratio of almost ten (Sullivan, 2005). The substantial support for family history in schizophrenia susceptibility suggests that familial determinants can provide clues on the etiology of schizophrenia. The familial determinants could be related to life-style and/orenvironmental exposure and/or the heritable genetic susceptibility. Other risk factor and odd ratios to develop schizophrenia are as illustrated in Figure 1.1.

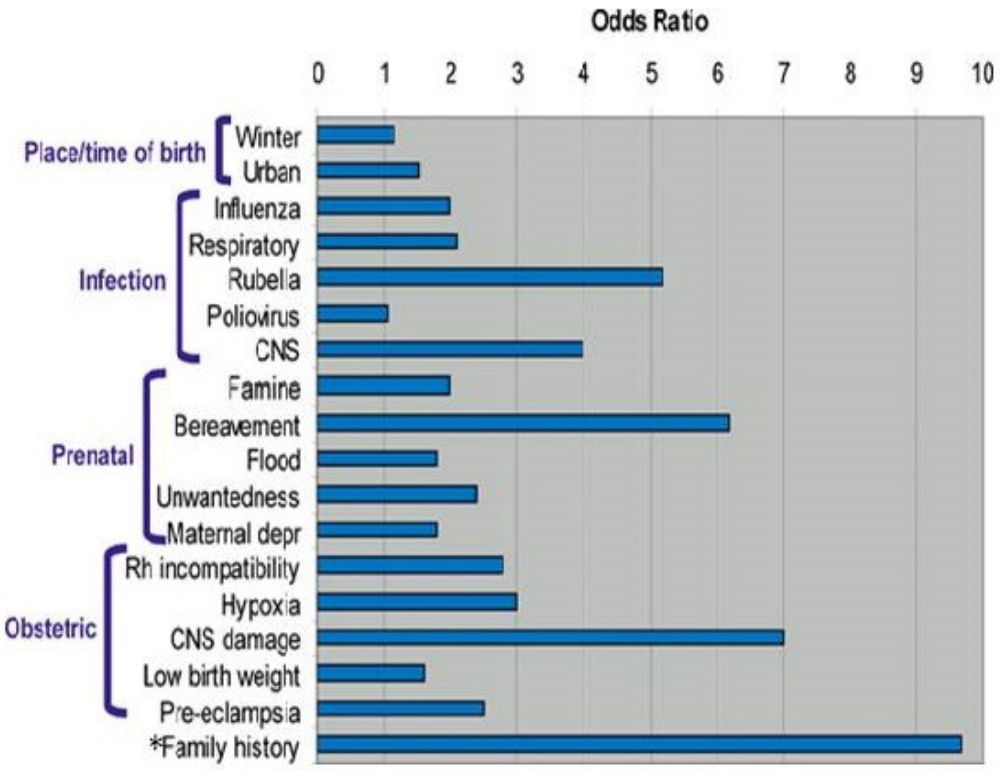

Figure 1.1: Comparison of a Selected Set of Relatively Well-Established Risk Factors for Schizophrenia (abbreviations: CNS: central nervous system; depr: depression; Rh: Rhesus). A ten-fold likeliness for schizophrenia in persons with first degree family history of schizophrenia*.Source: The Genetics of Schizophrenia (Sullivan, 2005).

1.2.2.1 Pathophysiology of Schizophrenia.

As any other complex diseases, schizophrenia is thought to arise due to multiple predisposing factors, both genetic and non genetic. Evidence presented by two breakthrough papers published more than 20 and 10 years ago respectively, on the important of combined effects of genetic and non-genetic factors for schizophrenia have remained solid until the present day (Kiberstis & Roberts, 2002; Lander & Schork, 1994).

There are several theories on the pathophysiology of schizophrenia. The theories involve a numbers of risk factors that present early in life. Among the risk factors include maternal malnutrition, maternal infection and delivery complications

(D. A. Lewis & Levitt, 2002).Interestingly, both advanced paternal age and young paternal age at conception are associated with increased risk of schizophrenia(Miller, Messias, Miettunen, Alaraisanen, Jarvelin, Koponen, Rasanen, Isohanni, & Kirkpatrick, 2011). To date there is no single theory of schizophrenia that prevails over the rest. Lakhan and Viera (2009) in their extensive review of pathophysiology of schizophrenia had listed more than fifteen pathophysiological models of schizophrenia. Some of the models include the disruption of neurotransmitter pathways of dopamine and glutamine, the famous neurodevelopment hypotheses, cognitive deficiency, genetic inheritance and abnormalities in several molecular pathways such as DISC-1 (Lang et al., 2007)(Figure 1.2).

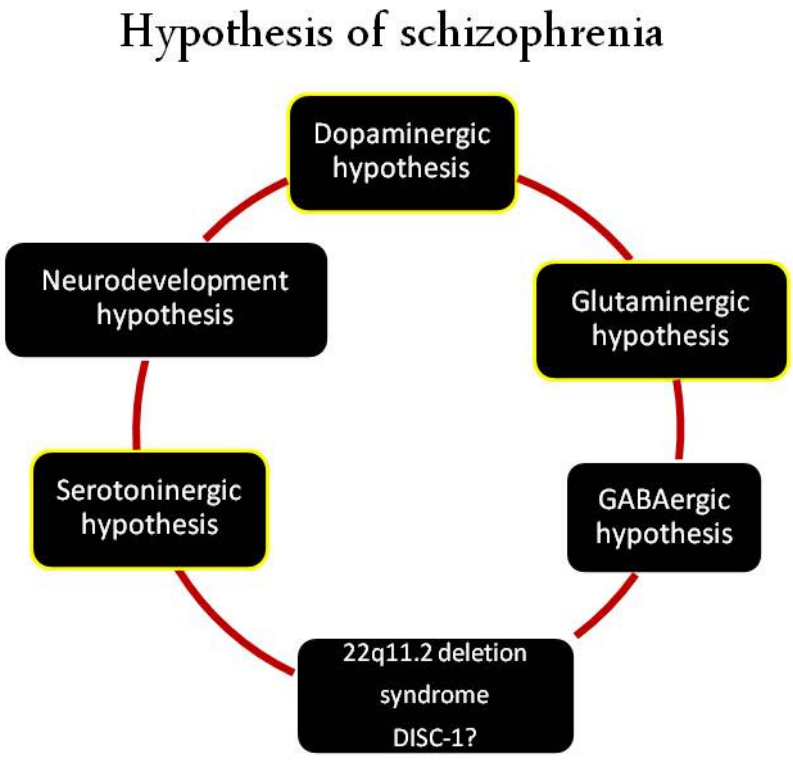

Figure 1.2: Hypothesis of schizophrenia based on molecular mechanism of schizophrenia. Figure constructed based on a review article by Lang et al., (2007)

The early hypothesis on the disruption of dopamine neurotransmitter pathway in schizophrenia is based primarily on pharmacologic evidence. This hypothesis has dominated theories on schizophrenia for more than 50 years. In the late 1960s, Van Rossum hypothesized that hyperactive dopamine transmission is the cause for the disorder (P. Seeman, 1987). As most of the clinically effective anti-psychotic drugs, either typical anti-psychotics or atypical anti-psychotics, block the dopamine D_2 receptors, the hypothesis seems most plausible and established. Additionally, supporting evidence also came from a number of observational studies that found psychotic manifestations in participants treated with an amphetamine. Amphetamine is a dopamine agonist. These manifestation is relieved upon treatment with dopamine-D_2 receptors blocking agents (Meltzer & Stahl, 1976).

The neurodevelopment hypotheses of schizophrenia proposed that brain abnormalities arise early in life and remain dormant until the pruning of neural connections (R. M. Murray & Lewis, 1987). There was also suggestion that linked the neurodevelopment hypothesis with a dysfunction at the glutaminergic neurotransmitter pathway. It is also reported that shifts of the NMDA receptor subunit result in the transition from juvenile to "adult" neural processing in many brain regions (Dumas, 2005; Henson, Roberts, Perez-Otano, & Philpot, 2010).

Unraveling the pathogenesis of schizophrenia is critical for efforts at the prevention of schizophrenia. Additionally, deciphering the pathophysiology of schizophrenia is essential for the identification of novel targets for future therapeutic intervention (David A. Lewis, 2002).Both pathogenesis and pathophysiology knowledge of schizophrenia are important to understand better this extremely complex mental disorder.