بسم الله الرحمن الرحيم

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تم عمل المسح الضوئي لهذة الرسالة بواسطة / حسام الدين محمد مغربي

بقسم التوثيق الإلكتروني بمركز الشبكات وتكنولوجيا المعلومات دون أدنى مسئولية عن محتوى هذه الرسالة.

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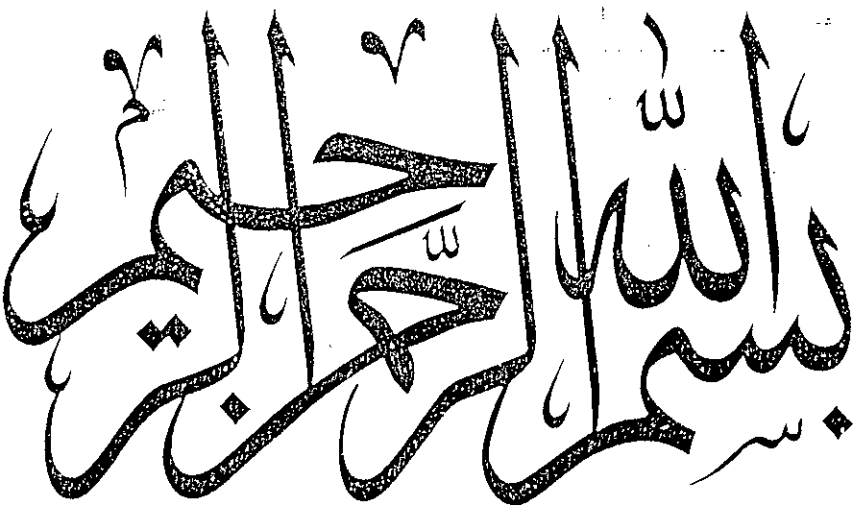
بسم الله الرحمن الرحيم

OBSESSIVE COMPULSIVE SYMPTOMS IN PATIENTS WITH SCHIZOPHRENIA

Thesis

Submitted to the
Faculty of Medicine
University of Alexandria
in Partial Fulfillment
of the requirements for the Degree of

Master of Psychiatry & Neurology

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2001

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INTRODUCTION

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History:

Schizophrenia dated to the very early reports written about medicine and its symptoms were the ground for many superstitions, it took a lot of time to be recognized as it is already known, one of the very early reports was given by "Soranus" who described delusions in persons who "believe themselves to be Gods" that are now known as delusions of grandiosity. Only in the last three centuries the diseases was taken as a pathological category and has been the subject of intensive research work. [1]

The French psychiatrist "Benedict Morel" gave the term "demence precoce" describing mental disturbance started in adolescence. Later two other psychiatrists described other features, "Karl Ludwig Kahlbaum" described catatonia that he considered a structural brain disease, and "Ewold Hacker" who described hebephrenia, and considered it a progressive disease of puberty and adolescence. [1]

"Emil Kraeplin" translated Morel's term to dementia precox, that to say cognitive disturbance starts with early onset and patients with the disorde: ran in deteriorating course with prominent delusions and hallucinations. Kraeplin clearly described signs and symptoms of schizophrenia, its clinical course, and outcomes: he also classified the disease into four types. [2]

"Eugen Bleuler" who was the first one to introduce the term schizophrenia attributed the disease to brain pathology but that in some cases there was no pathological brain process only a mild quantitative deviation of brain function from the normal. [3]

"Sigmund Freud" postulated that schizophrenia resulted from developmental fixations that occurred earlier than those culminating in the development of neuroses, Freud also postulated that an ego defect contributed to the symptoms of schizophrenia, ego disintegration in schizophrenia represents a return to the time when the ego was not yet, or had just begun to be, established. [4]

Unlike Freud "Harry Stack Sullivan" engaged schizophrenic patients in intensive psychoanalysis and concluded that the disorder was caused by early interpersonal difficulties, particularly those related to what he considered faulty, overanxious mothering. [4]

"Kurt Schneider" was one of the first psychiatrists tried to make reliable diagnosis of schizophrenia and put diagnostic criteria for the disease that has been called after his name. [5, 6]

Schneider's rank symptoms of schizophrenia:

1. First-rank symptoms

- Audible thoughts.
- Voices arguing or discussing or both.
- Voices commenting.
- Somatic passivity experiences.

- Thought withdrawal and other experiences of influenced thought.
- Thought broadcasting.
- Delusional perceptions.
- All other experiences involving volition, made affects, and made impulses.

2. Second –rank symptoms

- Other disorders of perception.
- Sudden delusional ideas.
- Perplexity.
- Depressive and euphoric mood changes.
- Feelings of emotional impoverishment.
- "...and several others as well".

Definition:

According to Diagnostic and Statistical Manual of Mental disorders (DSM-IV)[7] schizophrenia is defined as a disturbance that lasts for at least 6 months and includes at least one month of active-phase symptoms (that is, two [or more] of the following; delusions, hallucinations, disorganized speech, grossly disorganized or catatonic behavior, negative symptoms). [4]

According to WHO schizophrenia is a group of psychoses in which there is a fundamental disturbance of personality, a characteristic distortion of thinking, often a sense of being controlled by alien forces, delusions that may be bizarre, disturbed perception, abnormal affect out of keeping with real situation, and autism. Nevertheless, clear consciousness and intellectual capacity are usually maintained. [8]

The disturbance of personality involves its most basic functions, those that give the normal person his feeling of individuality, uniqueness, and self-direction. [8]

Epidemiology:

The incidence of schizophrenia is defined as the number of new cases in a given population, usually per 1000 persons, during a specific period of time (1 year by convention). In an illness with an insidious onset, such as schizophrenia, accurate incidence rates can be difficult to determine. [9]

Because schizophrenia is a chronic illness, the incidence rates must, by definition, be much lower than the prevalence rates. Prevalence is defined as the number of cases present in a specified population at a given time or time interval (e.g., at a specific point in time, during a time period, or over a lifetime). Lifetime prevalence represents the proportion of persons who have ever had the illness at a given time. [10, 11]

Lifetime prevalence rates of schizophrenia, based on the Epidemiological Catchment Area (ECA) data, were approximately 1% (range across three sites, 1.0% to 1.9%) [12], Point prevalence rates based on International Pilot Study of Schizophrenia data showed no significant differences across study centers: schizophrenia was found universally with relatively equal frequencies in a wide variety of cultures. [8]

A large body of data suggests that although men and women have an equivalent lifetime risk, the age at onset varies with sex. Although some sites showed different prevalence rates of schizophrenia in men and

women, the overall prevalence rates, as reported in the ECA survey, did not differ significantly between sexes[13], However, there is some evidence that onset of schizophrenia is generally several years earlier in men than in women [14], Therefore, incidence and prevalence rates of schizophrenia across sexes may vary according to age, with mean age is 15 to 25 years for men and 25 to 35 years for women it is rare before age of 10 and after age of 50, the prognosis is better in women than in men.[4]

Etiology:

It has been proposed that more than one causative mechanism might interact (the so-called double-hit hypothesis) to cause the illness in some individuals.

*** Genetic theory:**

Schizophrenia represents a difficult object for genetic science for several reasons:

- The paucity of extended multigenerational family histories containing large numbers of affected individuals.
- The possibility of genetic heterogeneity, such as more than one phenotype or more than one genetic variant.
- The lack of agreement on the mode of transmission.[9]

In studies of adopted monozygotic twins, twins reared by adoptive parents are seen to have schizophrenia at the same rate as their twin siblings brought up by their biological parents, this finding suggests that the genetic influence outweighs the environmental influence, a finding

corroborated by the observation that the more severe the schizophrenia, the more likely the twins are to be concordant for the disorder. [14, 15, 16]

Twin studies available data indicate that the concordance of schizophrenia among dizygotic twins is approximately 8% to 12 %, this is much greater than the 1% rate found in the general population and comparable to the rate of concordance of schizophrenia among first-degree siblings, the concordance of schizophrenia among monozygotic twins is approximately 50%. [17]

Now efforts are directed towards identification of the gene or genes responsible for production of schizophrenia symptoms; the human genome project is establishing a set of markers for the entire genome for schizophrenia linkage. It should be noted that genetic markers mark a segment of DNA presumably where the gene of interest resides; they do not necessarily identify mutant genes themselves. Once linkage is established, the second stage of work begins, which entails searching the identified segment of DNA for the faulty gene. [9]

In contrast, association studies actually use the candidate genes themselves and test the highly specific hypothesis that a mutation in the candidate gene occurs at a greater rate in the population of interest (in this case schizophrenic patients) than in non-affected control populations. [9]

One limitation of this approach is that it is all or none; that is, the candidate gene either is or is not associated with the illness. As there may be 100,000 genes in the human genome, selecting the "schizophrenia gene(S)" is a daunting task.[9]

Many associations between chromosomal sites and schizophrenia have been reported since the application of the techniques of molecular biology became widespread. More than half of all chromosomes have been associated with schizophrenia in various reports, but the long arms of chromosomes 5,11, and 18, the short arm of chromosome 19, and the X chromosome have most commonly been implicated, other reports of suggestive linkage on chromosomes 1 and 3. [9, 18]

In all cases, there has been a failure to replicate these findings. It has become painfully clear that the replication studies are, in many ways, more important to establishing linkage than the initial report. A linkage to chromosome 6 is being investigated by a large number of independent research groups, with promising preliminary results, Genes that have been found not to be associated with schizophrenia include the dopamine D_2 and D_4 genes. [9]

* **Viral theory:**

Two lines of evidences that have provoked the most interest in the possibility that viral infections are causative of schizophrenia are an increase in birth during influenza epidemics of individuals who subsequently develop schizophrenia and an increase in winter births among patients with schizophrenia because of the higher rate of viral infections in winter months. [9, 19]

"Mednick" and colleagues reported a strong association between pregnancies during the 1957 influenza epidemic in Helsinki, Finland, and subsequent development of schizophrenia. [14] Moreover, it was learned that the relationship between viral exposure and schizophrenia appears

strongest when exposure occurred during the second trimester of pregnancy. This is of interest because the second trimester is a critical period for critical and limbic development. [20]

It was therefore reasoned that second-trimester viral exposure might disrupt neuronal development in key areas of the brain, such as the hippocampus and prefrontal cortex, which have been implicated in this illness. In fact, there is some experimental evidence from animal models that viral exposure to these regions in the developing brain produces neuropathological changes resembling those observed in some postmortem studies of schizophrenia. [9]

Several studies have demonstrated an excess of winter births among patients with schizophrenia. Although statistically significant, the association between winter births and schizophrenia appears relatively small, occurring in less than 10% of cases. [18]

* Neurochemical disturbance in schizophrenia

Dopamine

Dopamine is the most extensively investigated neurotransmitter system in schizophrenia. In 1973, it was proposed that schizophrenia is related to hyperactivity of dopamine. [21, 22] This proposition became the dominant pathophysiological hypothesis for the next 15 years. Its strongest support came from the fact that all the available antipsychotic agents have antagonistic effects on the dopamine D_2 receptor in relation to their clinical potencies. [23]

In addition, dopamine agonists, such as amphetamine and methylphenidate, exacerbate psychotic symptoms in a subgroup of patients with schizophrenia. Moreover, as noted earlier, the most consistently reported postmortem finding in the literature of schizophrenia is elevated D_2 receptors in the striatum. [9]

The dopamine hyperactivity hypothesis has now undergone its greatest challenge. The primacy of D_2 antagonism for antipsychotic drug action has been seriously questioned largely because of the advent of Clozapine, an atypical antipsychotic drug, [23, 24] which has proved to be the most efficacious treatment for chronic schizophrenia and yet it has the lowest levels of D_2 occupancy of all antipsychotic drugs. [24]

In vivo brain imaging studies have demonstrated Clozapine D_2 occupancy levels as low as 20% in patients deriving excellent antipsychotic efficacy (compared with more than 80% D_2 occupancy for haloperidol). [25]

In addition, there has been no direct confirmation of a dopamine dysfunction in this illness. Studies of cerebrospinal fluid levels of dopamine and its metabolites have not shown consistent changes compared with control values. [26]

Also, with the exception of one study by the Johns Hopkins Positron Emission Tomography (PET) group, who found elevated D_2 receptors in neuroleptic-naive and neuroleptic-withdrawn patients with schizophrenia, other brain imaging groups have failed to replicate abnormalities in D_2 receptor number. [27, 28]

Five subtypes of dopamine receptor have now been discovered, D_1, D_2, D_3, D_4, and D_5, and interest in dopamine receptors other than the D_2

receptor has arisen. The D_4 receptor is particularly intriguing as a pathophysiological candidate for schizophrenia. [28, 29, 30]

Clozapine has differential affinity for this receptor. In addition, it occurs at high densities in the neocortex and limbic system, two brain regions hypothesized to mediate the symptoms of schizophrenia. In contrast, as noted earlier, the D_2 receptor is present at low levels in neocortex and limbic systems and in high densities in the dorsal striatum, which is believed to mediate the extrapyramidal side effects of neuroleptic drugs. [30]

Elevated D_4 levels were found in postmortem brains of patients with schizophrenia, although these increase were in the basal ganglia, where D_4 receptors are in relatively low density and of questionable functional significance. D_4 antagonists are being developed for clinical trials in this illness. [28, 29]

Clinical trials of dopamine agonists have resulted in improvements in the negative symptoms of schizophrenia. A new model of dopamine dysfunction that has been reported states that deficits in dopamine, perhaps in the prefrontal cortex, may result in negative symptoms and that concomitant dopamine dysregulation in the striatum, perhaps related to faulty presynaptic control of dopamine release, may be involved in positive symptoms. This bi-directional model is under investigation. [31]

Serotonin

Interest in serotonin as a pathophysiological candidate in schizophrenia arose in the 1950s with the discovery that the hallucinogen lysergic acid diethylamide (LSD) had primary effects on serotonin