SCHIZOPHRENIA - AN OVERVIEW & ITS MANAGEMENT

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ABSTRACT

Antipsychotic medications have been available since the mid-1950s. They have greatly improved the outlook for individual patients. These medications, however; should be carefully handled and their choice and use should be optimized to allow the patient to function more effectively. Pharmacotherapy of schizophrenia should always aim at reducing the psychotic symptoms with exposure to the least drawbacks of drugs. This short review will discuss different clinical subtypes and course of schizophrenia. On the other hand, it will shed the light on new approaches in management of schizophrenia.

INTRODUCTION

Psychosis is an impaired ability to perceive reality, which may result in delusions and hallucinations together with other symptoms. Among psychotic disorders, schizophrenia has always occupied a major part and represents a source of bewilderment throughout recorded history. Those suffering from the illness once were thought to be possessed by demons and were feared, tormented, exiled or locked up forever. In spite of advances in the understanding of its causes, course and treatment, schizophrenia continues to confound both health professionals and the public. It is easier for the average person to cope with the idea of cancer than it is to understand the odd behavior, hallucinations or strange ideas of the person with schizophrenia. Expectations become more realistic as schizophrenia is better understood as a brain disease that requires ongoing treatment. Demystification of the illness, along with recent insights from basic neuroscience, gives new hope for finding more effective treatments for an illness that previously carried a grave prognosis.

Management of schizophrenia is a protracted or more precisely a life time process that requires effective pharmacotherapy along with other lines of supportive therapy especially psychotherapy. Control of the disease may become a difficult target as other health challenges interfere. Schizophrenic patients may suffer co-morbid conditions especially diabetes mellitus, increased weight and serious cardiovascular disorders. On the other hand, symptoms of the disease not only affect the patients but also affect their families and “surroundings”. Therefore, it is sometimes important for physicians to provide guidance to all persons affected by the disease. Psychosocial and family interventions can improve outcomes.

SYMPTOMS AND TYPES OF SCHIZOPHRENIA

Schizophrenia is a devastating chronic psychotic illness that impairs mental and social functioning. It affects about one percent of the population in all cultures with equal incidence in males and females. Onset typically occurs in adolescence or young adulthood, but it usually develops later in women than in men. Schizophrenia results in fluctuating, gradually deteriorating, or relatively stable disturbances in thinking, behavior, and perception. Severity can range from mild and subtle with very good adaptation to everyday life, to severely disabling requiring constant supervision in a restricted environment. In advanced cases, the illness profoundly disrupts the lives of patients as well as their families and friends.

Schizophrenia is characterized by positive and negative symptoms that can influence a patient's thoughts, perceptions, speech, affect, and behaviors. Positive symptoms include hallucinations, voices that converse with or about the patient, disorganized speech and behavior, agitation and delusions that are often paranoid. On the other hand, negative symptoms may include poverty of speech, flattened affect, loss of sense of pleasure, lack of will or drive, and social withdrawal. Schizophrenia is also characterized by disorganized thought, which is manifested in speech and behavior. Disorganized speech may range from loose associations and moving quickly through multiple topics to speech that is so muddled that it resembles schizophasia (commonly referred to as "word salad"). Schizophasia is speech that is confused and repetitive, and that uses words that have no apparent meaning or relationship to one another. Disorganized behavior may lead to difficulties in performing daily living activities, such as preparing a meal or maintaining hygiene. It also can manifest as childlike silliness or outbursts of unpredictable agitation.

The clinical picture of schizophrenia differs 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.

Paranoid Subtype

The defining feature of the paranoid subtype is the presence of auditory hallucinations or prominent delusional thoughts about persecution or conspiracy. However, people with this subtype may be more functional in their ability to work and engage in relationships than people with other subtypes of schizophrenia.

Disorganized Subtype

As the name implies, this subtype’s predominant feature is disorganization of the thought processes. As a rule, hallucinations and delusions are less pronounced, although there may be some evidence of these symptoms. These

people may have significant impairments in their ability to maintain the activities of daily living. Even the more routine tasks, such as dressing, bathing or brushing teeth, can be impaired or lost. Often, there is impairment in the emotional processes of the individual.

Catatonic Subtype

The predominant clinical features seen in the catatonic subtype involve disturbances in movement. Affected people may exhibit a dramatic reduction in activity, to the point that voluntary movement stops, as in catatonic stupor. Alternatively, activity can dramatically increase, a state known as catatonic excitement. Other disturbances of movement can be present with this subtype.

Undifferentiated Subtype

The undifferentiated subtype is diagnosed when people have symptoms of schizophrenia that are not sufficiently formed or specific enough to permit classification of the illness into one of the other subtypes. The symptoms can fluctuate at different points in time, resulting in uncertainty as to the correct subtype classification. Other people will exhibit symptoms that are remarkably stable over time but still may not fit one of the typical subtype pictures. In either instance, diagnosis of the undifferentiated subtype may best describe the mixed clinical syndrome.

Residual Subtype

This subtype is diagnosed when the patient no longer displays prominent symptoms. In such cases, the schizophrenic symptoms generally have lessened in severity. Hallucinations, delusions or idiosyncratic behaviors may still be present, but their manifestations are significantly diminished in comparison to the acute phase of illness.

COURSE OF THE DISEASE

Family history

A family history of schizophrenia is the most significant risk factor [17, 23]. People who have a close relative with schizophrenia are more likely to develop the disorder than are people who have no relatives with the illness. For example, a monozygotic (identical) twin of a person with schizophrenia has the highest risk (40 - 50 %) of developing the illness. A child whose parent has schizophrenia has about a 10 percent chance. By comparison, the risk of schizophrenia in the general population is about 1 percent.

Genetic role

The Finnish Adoptive Family Study of Schizophrenia has confirmed that genetics plays a major role in the development of schizophrenia [35]. It also found that persons with a genetic risk of schizophrenia are especially sensitive to the emotional climate of their family environment. A child-rearing environment with infrequent criticism and clear, straightforward communication appears to be protective against the symptomatic expression of this genetic risk [35].

Role of central neurotransmitters

Neurotransmitters, substances that allow communication between nerve cells, have long been thought to be involved in the development of schizophrenia. It is likely, although not yet certain, that the disorder is associated with some imbalance of the complex, interrelated chemical systems of the brain, perhaps involving the neurotransmitters dopamine and glutamate. Interestingly drugs that cause psychoses similar to the positive symptoms of schizophrenia increase dopaminergic neurotransmission and almost all antipsychotics decrease dopaminergic neurotransmission [5]. However, still dopaminergic pathways cannot entirely explain the pathophysiology of schizophrenia, and the roles of other neurotransmitters are being investigated.

Possible role of physical brain abnormalities

Many studies of people with schizophrenia have found abnormalities in brain structure (for example, enlargement of the fluid-filled cavities, called the ventricles, in the interior of the brain, and decreased size of certain brain regions) or function (for example, decreased metabolic activity in certain brain regions).

It should be emphasized that these abnormalities are quite subtle and are not characteristic of all people with schizophrenia, nor do they occur only in individuals with this illness. Microscopic studies of brain tissue after death have also shown small changes in distribution or number of brain cells in people with schizophrenia. It appears that many (but probably not all) of these changes are present before an individual becomes ill, and schizophrenia may be, in part, a disorder in development of the brain.

Developmental neurobiologists funded by the American National Institute of Mental Health (NIMH) have found that schizophrenia may be a developmental disorder resulting when neurons form inappropriate connections during fetal development. These errors may lie dormant until puberty, when changes in the brain that occur normally during this critical stage of maturation interact adversely with the faulty connections.

Other risk factors

Some hypothetical risk factors include prenatal difficulties like intrauterine starvation, maternal viral infections, season and location of birth as well as socioeconomic status. However, data supporting these ideas are inconclusive [2, 23].

NOVEL APPROACHES TO THE TREATMENT OF COGNITION IN SCHIZOPHRENIA

In optimally treated people with schizophrenia, poor psychosocial function correlates not with residual psychotic symptoms, but rather with cognitive dysfunction [10]. Poor executive function predicts low overall community function, low vigilance, poor social skills, memory deficits, and poor overall outcome. Indeed, it has become clear, just focusing on positive symptoms, that satisfactory treatment exists for psychosis. It is increasingly recognized that cognition, on the other hand, is not appreciably affected by antipsychotic medication,

and this observation has redirected the focus of experimental therapeutics on the discovery of treatment targets and compounds to augment cognitive function in the illness [4].

The target most favored for cognition is augmentation of central cholinergic function (i.e., nicotinic and/or muscarinic acetylcholine receptors). The highest densities of nicotinic acetylcholine receptors (nAChRs) are in the medial temporal lobe, an area known to be important in schizophrenia pathology; expression of the 7 nicotinic receptor appears to be reduced in the illness. Administration of a partial nicotinic agonist has shown promise in reversing some aspects of cognitive dysfunction [24]. Muscarinic acetylcholine receptors (mAChRs) are also compelling targets for cognitive improvement in schizophrenia for a number of reasons especially their efficacy (albeit of small magnitude) in Alzheimer's disease (AD); and the cognitive decline that occurs with muscarinic antagonist treatments. Selective muscarinic agonists are being tested for therapeutic effects in schizophrenia.

Drugs that enhance glutamatergic plasticity in brain, especially acting at or affecting the N-methyl-D-aspartate (NMDA) receptor, provide a strong rationale for improving cognition. Augmentation of NMDA signaling can improve cognition. Ketamine, an NMDA antagonist, adversely affects cognition in normal and schizophrenic persons [15]. Candidates for cognitive enhancement acting through the NMDA receptor include the amphakines, D-serine, blockers of glycine reuptake, and drugs that affect mGlu receptors. An example of this latter type, the mGlu2/3 receptor agonist LY2140023, has already demonstrated antipsychotic activity and a profile favorable for cognitive enhancement [25].

Polyunsaturated fatty acids and antipsychotic action

The phospholipid hypothesis of schizophrenia, originally developed by David Horrobin and his colleagues [12, 27] proposed that a variety of mental health problems could result from abnormalities of the phospholipid structure of neuronal membranes. Omega-3 fatty acids are primarily obtained from dietary sources. The parent of this class of fatty acids is A-linolenic acid (ALA). This fatty acid cannot be synthesized by humans, so it is termed an essential fatty acid. The omega-3 fatty acids which have been investigated most in relation to mental health are eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA). Although these fatty acids can be synthesized from ALA, the metabolic pathway is not very efficient [3] so that in practice most EPA and DHA come from dietary sources, particularly fish.

DHA is a major omega-3 polyunsaturated fatty acid in the phospholipid of neuronal cell membranes [13]. EPA, in contrast, is not present in neuronal cell membranes. Because of this, DHA and EPA have different physiological effects on neuronal function. Thus, there is good evidence that changing the DHA content of neuronal cell membranes can alter densities of dopamine, serotonin and muscarinic receptors in brain [6]. EPA can affect neuronal function because it is an important precursor of eicosanoids and modulator of cytokines which have neurotransmitter and neuromodulatory effects [7]. It has been shown repeatedly that schizophrenic patients have reduced cell membrane levels of polyunsaturated fatty acids, particularly DHA and arachidonic acid (AA) [28].

Use of omega-3 poly-unsaturated fatty acids especially EPA in schizophrenia has shown significant improvement in both schizophrenic symptoms and tardive dyskinesia [26]. Interestingly clozapine, one of the atypical anti-psychotics, has been shown to increase the concentration of such fatty acids in red blood cell membranes, thereby suggesting that atypical antipsychotics may contribute to the normalization of neuronal membrane function by increasing their polyunsaturated fatty acid content. Thus omega 3 fatty acids may provide an important and novel approach to the development of antipsychotics in the future.

Vitamin therapy and modulation of nutritional status as new targets of treatment of schizophrenia

There have been several studies showing that most schizophrenic patients eat a diet which is high in saturated fat and sugar, and low in polyunsaturated fats and in fresh fruit and vegetables. Therefore, they consume low levels of omega-3 fatty acids, folic acid and antioxidant vitamins, and excessive quantities of unhealthy foods [34]. This may explain the common biochemical findings of high homocysteine levels, low omega-3 fatty acid levels, and high oxidative stress [14] in these patients. Other studies have shown that many schizophrenic patients suffer from multiple nutritional deficiencies [11]. Therefore, it is likely that optimal nutritional treatment for schizophrenia should involve increasing the intake of multiple nutrients.

Vitamin therapy could benefit people with schizophrenia by preventing or reversing the symptoms of vitamin deficiency disease, or by normalizing disordered brain metabolism when administered in doses greater than required to prevent deficiency. Since the diet of people with mental illness is often extremely poor, it is quite likely that some of them suffer from vitamin deficiencies which could worsen their already disturbed brain function. Simple correction of unrecognized nutrient deficiencies could explain the improvements reported in mentally ill patients administered standard vitamin supplements [9, 29].

Subclinical folic acid deficiency increases plasma homocysteine concentrations which may participate to the etiology of schizophrenia [1, 16]. Clinical reports have described abnormal folic acid and vitamin B_{12} metabolism in some people with schizophrenia [32]. The addition of 15 mg/day of methyl folate to standard psychiatric therapy improves the clinical and social recovery of patients with acute schizophrenia [30].

Ascorbic acid deficiency is well known in chronic schizophrenia [21]. It is plausible that the pathologic process responsible for schizophrenia could increase ascorbic acid utilization [31]. Several studies have shown that the symptoms of chronic schizophrenia can be ameliorated by high-dose ascorbic acid therapy [5].

Pregnancy in women with schizophrenia

Most recent studies show comparable numbers of pregnancies for women with schizophrenia. However,

more of the pregnancies among women with schizophrenia are unplanned and unwanted [20]. As compared to healthy controls, women with schizophrenia report receiving less prenatal care, and are more likely to be a victim of violence when pregnant. Pregnancy appears to worsen mental health in women with schizophrenia particularly young patients [19]. As compared to pregnant controls without a history of psychosis, schizophrenic patients report more anxiety, material-situational and interpersonal problems, panic about delivery, and lack of confidence about their ability to parent [18].

Both positive and negative symptoms of schizophrenia may pose unique risks during pregnancy. Such symptoms can lead to delayed recognition of pregnancy, misinterpretation of signs of labor, attempts at premature self-delivery, and precipitous delivery [33]. Overall, women with schizophrenia have an increased risk of obstetric complications, including placental abnormalities and antepartum hemorrhages [22].

One especially high-risk symptom during pregnancy is psychotic denial of pregnancy. Pregnant women who maintain the delusion that they are not pregnant may refuse prenatal care. Some such women fail to recognize labor, and may have precipitous, unassisted deliveries.

SUMMARY AND CONCLUSIONS

Schizophrenia is a chronic brain disorder, with a lifetime risk of 1%. It is structurally and functionally coupled to several cortical and subcortical brain regions participating in cognitive, emotional and motivational behavior. Psychotic symptoms are divided into positive, such as delusion, hallucinations and disorganized speech; and negative symptoms, e.g. emotional pauperism and lack of motivation. There is a 10 percent lifetime risk of suicide in patients with schizophrenia. Though the etiology of schizophrenia regarding genetic and molecular biological aspects is hardly understood, there is a strong evidence that dysregulations in dopamine and other neurotransmitter systems are involved in the development of the disease.

During the past century management of psychosis has achieved undeniable progress and old hydro-therapy (i.e. pouring of cold water in a stream, from a height of at least four feet onto the forehead of the patient) has been replaced over-time by a wide range of antipsychotics drugs. Today, treatment of schizophrenia focuses on several typical and atypical neuroleptics, which mainly act as negative dopamine modulators in CNS.

The effects of anti-psychotic drugs can be mediated by dopamine D_2-like receptors (D_{2R}, D_{3R}), serotonin receptor (5-HTR) subtypes and/or the influence on the glutamatergic system. Atypical compounds show equivalent affinities at D_{2R}/D_{3R} and 5-$HT2_{AR}$/5-$HT2_{CR}$. 5-HT2R subtypes modulate dopamine levels in the corresponding neuronal systems. In tubero-infundibular and nigrostriatal tracts exclusive D_{2R}/D_{3R} antagonism may evoke an increase of negative symptoms and also of extra-pyramidal motoric and other side effects. 5-HT2R antagonism attenuates the dopaminergic inhibition, while it continues in mesolimbic and mesocortical pathways, where no 5-HT2Rs are expressed. Stimulation of dopamine release in the prefrontal cortex is associated with a therapeutic benefit in treating negative symptoms and cognitive impairment in schizophrenia.

As a result of extensive research to better understand causes of schizophrenic illness, novel approaches of treatment are focusing on new therapies as H_3 histamine receptor antagonists, omega 3 fatty acids and specific vitamin therapy particularly with folic acid, ascorbic acid and vitamin E.

As both types of schizophrenic symptoms in the patient may have a disturbing effect on his/her family; it is important for physicians to provide guidance to all persons affected by the disease. Psychosocial and family interventions can improve outcomes. Non compliance represents another challenge and a major reason of relapse. In addition the un-ignored fact is that present antipsychotic medication cannot generally be regarded as a “good treatment”, however it is just the best available and it should be used in most cases lifetime. Therefore extensive research is still going on in the hope of introducing more effective therapies that may be “curative” for this serious debilitating mental illness.

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