Biological Markers and the Future of Early Diagnosis and Treatment in Schizophrenia

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Early intervention is key in psychiatry because it may improve prognosis. This has been especially difficult with schizophrenia. There is a strong basis for schizophrenia as a neurodevelopmental disorder, and the illness may result from several factors: genetic inheritance, disturbance of the in utero environment, and exposure to biological and psychosocial factors in infancy and early childhood, to name a few. Early environmental risk factors for schizophrenia include urban and winter birth, fetal malnutrition and hypoxia, and prenatal viral infections; diverse risk factors such as paternal age, drug abuse, immigrant status, social adversity, and isolation also appear to be contributing factors.

The prodromal phase of schizophrenia has received a great deal of attention, and multiple biological markers have been identified that may allow earlier diagnosis and treatment of patients with the disease. Biological markers are defined as objective, measurable phenomena that may identify subjects at increased risk for development of disease and are often found not only in the patients but also in first-degree relatives. Biological markers may target etiology of the disease (risk factors for development of the illness), pathophysiology (abnormalities associated with the illness), or expression of the disease itself (manifestations of the illness). The Table summarizes some of the more common findings in schizophrenia based on the triad of etiology, pathophysiology, and disease manifestations.

We will review some well-known biological markers that have been studied, as well as ongoing research and where it is headed. The goal is to use biological markers to determine who is at risk for schizophrenia, to prevent the onset of schizophrenia in persons with prodromal symptoms, and, via early diagnosis and intervention, to reduce the severity of the illness in those who have schizophrenia.

Figure 1 outlines a hypothetical model of how schizophrenia may be viewed along a continuum from neurodevelopmental phenomena to disease expression and its influences.

ETIJOLOGY

Genetics
Schizophrenia is a common disorder with a lifetime prevalence of approximately 1%. It is highly heritable, but the genetics are complex. Study findings have consistently demonstrated that the risk to relatives of a proband with schizophrenia is higher than that to relatives of controls. On review of chromosomal studies, there seems to be a particularly increased focus of interest involving chromosome 22q11, chromosome 1q22, and chromosome 1q42.

One of the genes that has received the most attention is that involving catechol-O-methyltransferase (COMT). The story of the COMT gene enlightens the pathway between gene and phenotype. This gene is located on chromosome 22q11, and COMT participates in the clearance of dopamine from synapses, a functional polymorphism involving the presence of either valine or methionine altering enzyme activity. This protein product may be involved in regulation of neurotransmission related to schizophrenia. Studies evaluating the cognitive function of persons with different allele combinations at this gene have shown varying effects. Clinically, this information may help subcategorize patients, allowing for the tailoring of treatment to particular genetic types. One day, it may also provide the basis to screen for increased risk.

Environment
Numerous studies have demonstrated that persons born in the winter and spring months have a 5% to 8% excess risk for schizophrenia, both in the northern and southern hemispheres, particularly for those with a negative family history. Further evidence suggesting the action of environmental factors in at least some forms of schizophrenia comes from associations with latitude, urban birth,
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household crowding, birth order, and famine during pregnancy.¹

**Neurodevelopment**

Minor physical anomalies have consistently been identified in those with early-onset schizophrenia and have helped differentiate patients from controls. These signs of poor neurologic maturation include high-steepled palate, hypertelorism, large head circumference, small nasal volumes, and soft signs such as a positive glabellar tap.

**PATHOPHYSIOLOGY**

**Intellectual functioning**

A decline in scholastic abilities has been shown to identify children and adolescents in whom schizophrenia may develop.² Research in this area has traditionally focused on neuropsychological testing; studies have shown that first-degree relatives have subtle impairments in attention, verbal memory, executive function, and working memory.³,⁴

Working memory—the ability to maintain and use information in short-term memory modulated by the prefrontal cortex—has been the subject of increased focus, with deficits in working memory being reported in patients with schizophrenia. Harkavy-Friedman and associates⁵ evaluated the performance of patients with schizophrenia, their first-degree biological relatives, and nonpsychiatric controls and found that the patients were consistently impaired on working memory tasks. In contrast, their unaffected relatives were only impaired on working memory tasks with higher central executive processing requirements.

**Neuroimaging**

Neuroimaging is on the cutting edge of schizophrenia research as techniques and resolution advance. CT scans consistently show ventricular enlargement in patients with schizophrenia. Structural MRI studies have shown reductions in the prefrontal cortex, the hippocampus, and the amygdala in patients with schizophrenia.⁷

Positron emission tomography and single photon emission computed tomography techniques have been used to study neurotransmitter mechanisms. Magnetic resonance spectroscopy has also shown in vivo neurochemical changes in patients with schizophrenia, most notably a reduction in the concentration of N-acetylaspartate in the frontal and temporal cortical regions, indicating neuronal loss and supporting findings obtained using structural MRI studies of reduced gray matter in patients with schizophrenia.⁸

In their study using functional MRI (fMRI), Holt and colleagues⁹ demonstrated that hippocampal and amygdala activity is elevated in persons with schizophrenia during the passive viewing of human faces. An interesting avenue of research would be possible if this is identified as the underlying pathophysiology of persecutory delusions.

In addition, there have been some studies that measure the relationship of the changes of specific brain structures both anatomically and functionally before and after antipsychotic treatment.¹⁰ The combination of neuroimaging and psychopharmacology is another stimulating area of research attempting to tie neuroimaging techniques such as MRI and fMRI to psychopharmacologic development and implementation.

**Neurophysiology**

Eye tracking dysfunction (ETD) is a well-researched phenomenon that includes both the smooth pursuit and saccade systems. Saccades are very rapid movements used to move the eye quickly toward a target. During smooth pursuit, patients with schizophrenia follow a target slowly (ie, the speed of the eye is slowed in comparison to normal speed) and then show compensatory saccades to correct the error in eye position. Studies have shown that patients with schizophrenia and their family members have ETD.¹¹,¹²

Neurochemical findings of note include decreased plasma homovanillic acid (pHVA), the major metabolite of dopamine. Unfortunately, it is unclear whether and to what degree pHVA is a measure of central dopamine activity.¹³ Future neurochemical studies will focus on more specific proteins involved in dopamine uptake and metabolism in patients and unaffected relatives. One such example is the regulator of G protein signaling (RGS) molecules, which are a class of proteins that modulate the signaling activity of G protein coupled receptors. Because RGS4 is associated with the dopamine receptor, it is of particular interest in schizophrenia. RGS4 expression is altered in affected CNS tissue, and polymorphisms in the RGS4 gene are being examined as risk factors for the disease.¹⁴

Another interesting neurophysiologic response in schizophrenia is prepulse inhibition (PPI) of startle. Reduced or abnormal PPI in schizophrenia is among the most consistent markers of brain-based inhibitory deficits in this disorder; however, studies vary in their findings. Cadenhead and colleagues¹⁵ showed that patients with schizophrenia, their relatives, and subjects with schizotypal
personality disorder all had abnormal PPI relative to comparison subjects. Others report deficient PPI only in symptomatic patients that partially or completely resolves with medication treatment. It is hoped that further research will clarify these issues and that the clinical usefulness of measuring PPI in screening or treatment will be found.

**DISEASE MANIFESTATIONS**

Endophenotypes, a subset of biological markers, are measurable components unseen by the unaided eye. They can be neurophysiologic, biochemical, endocrinologic, neuroanatomic, cognitive, or neuropsychological in nature. As described by Prathikanti and Weinberger, to be considered an endophenotype, the putative deficits that compromise the endophenotype must be stable over time. The deficits should be found in mildly ill and psychiatrically healthy relatives to establish that these phenotypes are related to risks for the illness rather than being a result of the illness.

Figure 2 indicates the multiple sources of influence from gene to phenotype in a schematic that incorporates the above factors and how the disease of schizophrenia may manifest itself in multiple ways.

**DISCUSSION**

Discovering ways to put findings into practice will be the challenge in the future, not only to predict risk of disease but also to use changes in biomarkers to monitor response to treatment. One of the ways this will likely be done is by correlating the various biological markers, thereby strengthening the ability to predict risk. Investigators in Europe, particularly in Germany, are starting to address these issues.

The European Prediction of Psychosis Study is the first large European multicenter study that is focused on early detection of persons at risk for psychosis, particularly schizophrenia; it incorporates the use of biological markers. Compton and colleagues found that impairments in olfactory identification and verbal memory appear to represent 2 correlated risk markers for schizophrenia. They hypothesized that frontotemporal deficits likely account for both impairments. In summary, the goal is to use biological markers to determine who is at risk for schizophrenia and perhaps to prevent the onset of schizophrenia in people with prodromal symptoms or reduce the severity of the illness in those who have schizophrenia via early diagnosis and aggressive intervention. Yet we need to be mindful of the ethical dilemmas; those who are shown to have a propensity for schizophrenia must not be marginalized or discriminated against. Finally, we can use this information to understand the complex interplay between biological and environmental factors in the development and maintenance of this chronic disease and lower the burden on those living with schizophrenia.

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Evidence-Based References


Links: