Pathophysiologic Mechanisms in the Pathogenesis and Clinical Course of Schizophrenia

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It is widely accepted that schizophrenia originates from abnormalities occurring during the early stages of neural development. Although large studies have revealed behavioral precursors of schizophrenia in childhood, the disorder is usually not evident until patients are in their 20s or 30s. Some patients will be resistant to typical antipsychotic treatment at this first-onset of schizophrenia; however, treatment resistance develops in the majority of patients during the course of successive episodes. This ongoing deterioration suggests that a degenerative process operates during the active psychotic phase of the illness. This review presents evidence of neurodevelopmental and neurodegenerative mechanisms for the development of schizophrenia. These data indicate the importance of effective treatment at the first onset of schizophrenia to improve patient outcome. In addition, animal studies suggest that treatment with clozapine may prevent the neurodegenerative component responsible for the development of treatment resistance. (J Clin Psychiatry 1999;60[suppl 12]:9–12)

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chizophrenia typically develops in the early 20s in men and the late 20s to early 30s in women. A minority of patients are resistant to treatment with typical antipsychotics at onset; however, many patients become treatment resistant during subsequent episodes of the illness. Risk factors include a family history of schizophrenia and a fetal history of obstetric complications. This clinical course of schizophrenia and the identified risk factors have led to the belief that the diathesis occurs neurodevelopmentally during gestation from a combination of pathogenic factors and has a period of dormancy before the onset of symptoms. Nevertheless, some patients also seem to have the capacity for further limited neurodegeneration, which is presumably distinct from the neurodevelopmental diathesis that precedes it. This article reviews some of the evidence of a neurodevelopmental and a neurodegenerative mechanism in the development of schizophrenia. The therapeutic strategies for preventing these 2 forms of treatment resistance may need to be different, but research on the animal model suggests that pharmacologic treatment with atypical antipsychotic drugs may prevent the pathophysiologic process responsible for the neuroprogressive aspect of the illness.

THE DEVELOPMENT OF TREATMENT RESISTANCE

It is widely acknowledged (though not as yet proven) that schizophrenia originates from a disturbance in the earliest stages of neural development, during gestation and the early postnatal period. During this time, the nervous system is proliferating, differentiating, migrating to target locations, establishing synaptic connections, and producing refinements in viable cell populations and circuits that will be sustained into adult life. However, these neurodevelopmental abnormalities usually remain dormant during childhood and adolescence. Although some behavioral precursors, such as disordered motor development, have been identified in children who later develop schizophrenia, these differences are generally not severe enough or sufficiently specific to identify an individual patient before the onset of the illness.

Schizophrenia may have its origins in neurodevelopmental pathology, but only a small proportion of patients (10%–15%) are treatment resistant at the onset of the illness. However, between 30% and 60% of patients with schizophrenia eventually become treatment resistant or only partially responsive to treatment. Therefore, many patients seem to develop either the capacity to be unresponsive to treatment or a more severe form of the illness that no longer responds to treatment. These observations imply that there are 2 pathogenic processes for schizophrenia, a developmental process and a limited neurodegenerative process that underlies the progressive phase of the illness.

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An understanding of the relationship between the clinical course of schizophrenia, including the development of treatment resistance, and the underlying pathophysiology may reveal opportunities for therapeutic intervention to prevent the development of schizophrenia and of treatment resistance in patients who have already developed the disorder.

**EVIDENCE OF A NEURODEVELOPMENTAL MECHANISM**

A variety of etiologic factors have been suggested for schizophrenia. These include a genetic defect, an infection or immune response transmitted from the mother to the fetus across the placenta, and obstetric complications. All of these factors may affect the generation of nerve growth factors and their ability to stimulate viable cell development, by the stimulation of cytokines, infection, hypoxia, trauma, or stress-induced neurochemical effects. Thus, disturbances of processes involving neurotrophic factors during development may explain the underlying pathology of schizophrenia.1

A study of pregnant women who had been exposed to infection or physical trauma or were schizophrenic revealed an inverse relationship between gestational age and amniotic fluid levels of 3 different forms of nerve growth factors, brain-derived neurotropic factor (BDNF), neurotrophin-3 (NT-3), and nerve growth factor (NGF).4 Lower concentrations of nerve growth factors, particularly NGF, were evident in fetuses who had central nervous system (CNS) abnormalities or had been exposed to infection. Thus, NGF could be a marker for the process that results in limited or disrupted neural development in fetuses who develop schizophrenia in later life.

Imaging studies have identified abnormal brain morphology in schizophrenic patients. Studies using in utero ultrasonography have demonstrated that the lateral ventricles of some fetuses are enlarged as early as the third trimester of gestation and remain enlarged postnatally when examined in childhood with magnetic resonance imaging (MRI) (J. H. Gilmore, J. van Tol, H. Lewis-Streicher, et al., manuscript submitted.) This suggests that ventricular enlargement is a hallmark pathomorphologic feature of adult schizophrenia and can be detected in individuals long before the formal onset of the illness and as early as in utero. A comparison of patients who have first-episode schizophrenia with healthy controls also demonstrated that the ventricular volumes of the patients with schizophrenia were significantly larger, with significantly larger temporal horns than those of controls.5 In addition, the patients with first-episode schizophrenia showed relative reductions in left hippocampal volume compared with control subjects. Interestingly, first-episode patients with no ventricular enlargement are more responsive to treatment and have a faster rate of response.5

Studies conducted by Owen and colleagues have indicated an association between ventricular enlargement and obstetric complications.6 Patients whose birth was accompanied by severe obstetrical complications had a ventricular volume of 22 cc compared with 16.7 cc in patients with no history of severe obstetrical complications.7 This suggests that the enlargement of the ventricles is a consequence of the same phenomena that influence the likelihood to experience obstetric complications. In addition, patients with a history of severe obstetrical complications have a poorer treatment outcome, duration, and level of remission than patients without a history of such complications.7 Thus, enlarged ventricular volume and obstetrical complications may define a neurodevelopmental form of schizophrenia which comprises a phenotype that manifests poor outcome and poor response to conventional antipsychotic drug treatment.

**EVIDENCE OF A NEURODEGENERATIVE PROCESS**

The development of treatment resistance during successive episodes of illness suggests that schizophrenia has a progressive pathophysiologic component during the active psychotic phase of the illness that engenders treatment resistance. This is particularly evident in the early phase of the illness, the prodromal phase, and the 5 years immediately after the first episode of the illness.9 The time to remission increases in each successive psychotic relapse. In one study, mean group time to remission increased by 10 days in the second episode, and for those patients who had 3 episodes, there was a further substantial increase in time to remission.9 Thus, patients may be slightly less responsive to treatment during successive episodes or exacerbations, such that some residual symptoms remain as well as decrements in the patients’ functional capacity. Furthermore, first-episode patients with a longer duration of symptoms have lower and slower rates of remission than those with a shorter duration of symptoms, providing further support of a neurodegenerative process during the active psychotic phase of the illness.10 These studies indicate that patients should receive early effective intervention to prevent treatment resistance.

Neuroimaging studies have provided evidence of a neuropathologic basis of the development of treatment resistance. First-episode patients, who were largely treatment naive, were followed by MRI at baseline and 3 years later (reference 9 and J. H. Gilmore, J. van Tol, H. Lewis-Streicher, et al., manuscript submitted). There was no difference in change in ventricular volume between schizophrenic patients and healthy volunteers. However, if the patients were grouped by outcome, the good outcome patients (those who remitted and did not relapse) had a lower initial ventricular volume than those with a poor outcome (patients who did not remit or remitted but relapsed) and
showed no change in ventricular volume, whereas those with a poor outcome showed a significant increase in ventricular volume. Similar changes were also observed in cortical volume. Since these preliminary data were reported, 3 other groups have found similar results, all in young or first-episode patients. For example, Rapoport et al. found that the ventricular volume of a sample of patients with childhood-onset schizophrenia significantly increased between the baseline and 2-year follow-up, whereas there was no change in healthy controls. Similarly, patients with abnormal brain morphology, particularly of the lateral and third ventricles, take longer to reach remission.

Candidate theories for the potential neurodegenerative pathophysiologic processes involve dopamine projections to the cortex and glutamate projections from the cortex to subcortical structures, as evidenced by the psychotogenic effects of glutamatergic N-methyl-D-aspartate (NMDA) receptor antagonists. The synaptic regulation of dopamine is known to be impaired in patients with schizophrenia; therefore, an animal model of synapsin-knockout mice has recently been used to try to further understand this pathophysiology of schizophrenia.

Synapsins are a family of neuron-specific proteins that have been implicated in the development of synapses and neurotransmitter release. Three distinct genes for synapsin I, II, and III have been identified, each of which has been implicated in the pathophysiology of schizophrenia. Synapsins I and II also have distinct roles in synapse formation, whereas deletion of synapsin II retarded axon formation. Deletion of both synapsins led to partial restoration of the wild phenotype; however, the development of the neurons was delayed. This delay parallels the delay in reaching the adult phenotype observed in patients with schizophrenia. This animal model of synapsin-knockout mice is, like schizophrenia, development dependent and has elements of functional and trophic expression.

The atypical antipsychotic clozapine and the typical antipsychotic haloperidol have different effects in some animal models of schizophrenia. Rats were treated with saline or pretreated with either clozapine or haloperidol followed by an injection of ketamine, the NMDA receptor antagonist. Saline alone had no effect on the prefrontal cortical area; however, ketamine produced an increase in the uptake of 2-deoxyglucose in the prefrontal cortical area, indicating an increase in neuronal metabolism. Pretreatment with haloperidol enhanced the induction of 2-deoxyglucose, whereas pretreatment with clozapine blocked the induction of 2-deoxyglucose so that the animal appeared identical to that treated with saline alone. Similar effects occurred in the hippocampus: ketamine increased 2-deoxyglucose uptake in the dentate gyrus, which was accentuated by haloperidol but blocked by clozapine.

These results parallel the effects of clozapine and haloperidol on ketamine-induced psychotic symptoms in schizophrenic patients. Clozapine blunts ketamine-induced increases in positive symptoms in patients with schizophrenia, whereas haloperidol does not.

**CONCLUSIONS**

These preliminary and diverse lines of investigation suggest that schizophrenia has more than one pathophysiologic process and that there may exist more than one mechanism of developing treatment resistance. One may be neurodevelopmental, such that patients have a severe form of the illness and are nonresponsive to treatment from the onset, whereas other patients may become treatment resistant during successive episodes. The therapeutic strategies for preventing these 2 forms of treatment resistance may need to be different. Although it is unclear whether atypical antipsychotics can restore the neurodevelopmental deficits, research on the animal model suggests that clozapine, and possibly other atypical drugs, may prevent the pathophysiologic process responsible for the neuroprogressive form of the illness.

**Drug names:** clozapine (Clozaril, Leponex), haloperidol (Haldol and others).
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