Schizophrenia

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Abstract

Schizophrenia is a severe mental illness affecting several domains of cognition and behaviour. The illness most frequently becomes manifest in early adulthood, and often follows a chronic course. It is associated with high morbidity and mortality, and is a leading contributor to disease burden, health and social care costs throughout the world. Antipsychotics are the mainstay of treatment but are limited by significant adverse effects, and therapeutic options for many patients remain inadequate. Schizophrenia is associated with a range of adverse physical health outcomes, which can be compounded by lifestyle factors including substance use, barriers in accessing healthcare and the adverse effects of treatment. Psychological and social interventions are a crucial element of patient care, particularly in alleviating negative symptoms. Current theories view schizophrenia as a disorder of early brain development, with interacting genetic and environmental risk factors.

Keywords Antipsychotic; delusion; dopamine; hallucination; psychosis; schizophrenia

Key points

- Schizophrenia is a complex and often chronic illness requiring a coordinated multidisciplinary approach
- Early referral and treatment should be established in first presentations of psychosis
- Oral antipsychotics should be offered following a discussion with the patient of the relative risks and benefits. Polypharmacy should be avoided, and medication continued at the lowest effective dose
- Cognitive behavioural therapy should be offered to all patients, and family therapy to the relatives of people with schizophrenia
- Life expectancy in schizophrenia is significantly lower than that of the general population; co-morbid physical illness is overrepresented as a result of lifestyle factors and adverse effects of medication, and requires recognition and treatment
- Individuals with schizophrenia should be treated in a non-judgemental and compassionate manner, with an emphasis on promoting recovery and reducing stigma among patients, carers and the public

Definition

Schizophrenia is a mental illness characterized by positive symptoms (delusions, hallucinations, thought disorder, disorganized behaviour), negative symptoms (social withdrawal, apathy) and cognitive symptoms (poor executive function and memory). It frequently follows a chronic course and is associated with a decline in social and occupational functioning. International Classification of Diseases 10th revision (ICD-10) criteria for schizophrenia are listed in Table 1, and require a symptom duration of at least 1 month.

Epidemiology

The prevalence and incidence vary widely depending on the location and the diagnostic definition that is employed. Although it is often quoted that 1 in 100 of the population will have schizophrenia in their lifetime, studies suggest that the global average lifetime prevalence is somewhat lower, at 0.72%.[1] In a study of incidence of schizophrenia in England from 1997 to 1999, the age-adjusted incidence in Bristol was 7.2, in Nottingham 7.6 and in South-East London 20.1 cases per 100,000 person−years, suggesting geographical heterogeneity in underlying biological, psychological and environmental risk factors. The average general practitioner can expect to see around one new case per year, and have between five and 10 patients with the diagnosis on their caseload.

Schizophrenia usually emerges in late adolescence or early adulthood, with women having a later average age of onset than men. Onset is rare before the age of 16 years, and uncommon after age 50.

Pathophysiology

The *dopamine hypothesis* has played a central role in neurobiological theories of schizophrenia. Support comes from the observation that drugs such as amphetamines, which stimulate dopamine release, can induce psychosis, and that all antipsychotic drugs exert antagonism to D_2 dopamine receptors, with the degree of antagonism correlating with the therapeutic dose. Positron emission tomography and magnetic resonance imaging (MRI) ligand studies have demonstrated increased presynaptic dopamine synthesis and release during acute psychosis. However, approximately one-third of patients show a limited response to antipsychotic treatment, and recent findings suggest this subgroup may not exhibit dopaminergic dysfunction.

MRI studies have shown an overall decrease in brain volume of 3−4%, with particular differences in the volume of the hippocampi and thalamus, and enlargement of the lateral

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ICD-10 criteria for schizophrenia (F20)[a]

- At least **one** of the following:
  - Thought echo, thought insertion or withdrawal, or thought broadcast
  - Delusions of control, influence or passivity, clearly referred to body or limb movements or specific thoughts, actions or sensations; delusional perception
  - Hallucinatory voices giving a running commentary on the patient's behaviour, or discussing the patient between themselves, or other types of hallucinatory voices coming from some area of the body
  - Persistent delusions of other kinds that are culturally inappropriate and implausible (e.g. being persecuted by a network of government agents, being an emissary from another world)
- **Or** at least **two** of the following:
  - Persistent hallucinations in any modality, when occurring every day for at least a month, when accompanied by fleeting or half-formed delusions without a clear affective component, or when accompanied by persistent over-valued ideas
  - Neologisms, breaks or interpolations in the train of thought, resulting in incoherence or irrelevant speech
  - Catatonic behaviour, such as excitement, posturing or waxy flexibility, negativism, mutism and stupor
  - Negative symptoms such as marked apathy, paucity of speech, and blunting or incongruity of emotional responses
- Duration of the above symptoms for **at least 1 month**.

[a] ICD-10 classification of mental and behavioural disorders, diagnostic criteria for research.

Table 1

ventricles. At a cytoarchitectural level, an absence of gliosis and other correlates of cell injury or death strongly argue that schizophrenia is not due to a neurodegenerative process.

Aetiology

The *neuro-developmental hypothesis* of schizophrenia has gained widespread currency. This proposes that although the overt phase of illness is usually of adult onset, its roots lie in the preceding stages of brain development. The pathogenesis of schizophrenia is considered to depend on the interplay between genetic vulnerability and environmental and social factors.[2]

Genetic vulnerability

Monozygotic twin concordance rates for schizophrenia of about 50% point to a significant genetic basis, and current estimates suggest an overall heritability of around 80%. Nonetheless, most individuals who have been diagnosed with schizophrenia have no family history of psychosis, and no single genes have been identified, suggesting that many risk alleles of small effect size are involved. A landmark genome-wide association study identified 108 loci conferring risk for the disorder,[3] with notable associations with the *DRD2* dopamine-receptor gene and the major histocompatability complex coding region; this suggests a role for the immune system. A recent study provided further support for this hypothesis by demonstrating specific associations between the C4 complement gene and schizophrenia risk.

Polymorphisms in genes involved in neuronal migration (*DISC1*), synaptogenesis (neurexin family), and glutamate transmission have also received attention. New techniques that are able to detect deletions and duplications of chromosomal segments, known as *copy number variants* (CNVs), have revealed an over-representation of CNVs in schizophrenia, particularly in regions carrying genes involved in neuronal development. Recent studies have also demonstrated a shared genetic liability for schizophrenia and bipolar disorder, suggesting an aetiological continuum between them.

Gestational and perinatal exposures

A wide variety of prenatal exposures, such as viral or bacterial infection, stress and malnutrition, and perinatal variables, such as low birthweight, prematurity, prolonged labour and neonatal hypoxia, have demonstrated associations with an increased risk of schizophrenia. An intriguing finding is the modest but consistently raised incidence of schizophrenia among individuals born in the winter months, which may be causally related to a seasonal variation in rates of intrauterine viral infection.

Urbanicity, immigration and social adversity

Urban upbringing is associated with a more than twofold increase in risk of schizophrenia compared with rural settings, in a dose-dependent fashion. Various lines of evidence suggest this is not explained by a 'drift effect' of genetically vulnerable individuals moving to an urban setting, but by factors related to urban living, such as the physical environment and social disadvantage.

Consistently increased rates of schizophrenia are seen in first- and second-generation immigrants compared with non-migrants. It has been shown that the risk of developing schizophrenia is decreased among minority ethnic groups living in areas with a higher density of their own ethnic group. This suggests that the degree to which one occupies a 'minority position', with the associated chronic experiences of social marginalization, might be of aetiological importance.

Substance use

An expanding literature supports the hypothesis that cannabis increases the risk of developing schizophrenia. A systematic review found a dose-dependent increase in risk of long-term psychotic outcomes among those who had ever (odds ratio 1.41) or frequently (odds ratio 2.09) used cannabis. Recent research has identified a three-times excess risk among users of high-potency 'skunk', a form of cannabis containing a greater proportion of the active ingredient, tetrahydrocannabinol, than traditional