Schizophrenia

Schizophrenia is a chronic, frequently disabling neuro-developmental disorder with a collection of signs and symptoms of unknown aetiology, predominantly defined by psychosis that affects 1% of the world's population. In most common form, it presents with paranoid delusions and auditory hallucinations late in adolescence or in early adulthood.

History

- Late 19th century- Kraepelin defined "dementia praecox" or premature dementia as distinct from the insanity of tertiary syphilis or the cyclic, non-deteriorating psychosis of manic depressive illness.
- Early 20th century, Bleuler coined the term schizophrenia.
- 2nd half of the 20th century - considered a 'dopamine disorder' based on the psychosis-inducing effects of dopamine-releasing drugs (antipsychotic drugs that blocked dopamine D2 receptors)
  - Early neuroleptic meds have been increasingly replaced by antipsychotics that have fewer extrapyramidal side effects though not more efficacious. They could reduce delusions and hallucinations but not enhance functional recovery
- More recent hypothesis: schizophrenia as a 'glutamate disorder'.
  - Healthy volunteers given low doses of NMDA receptor antagonists (ketamine).
  - Some cognitive symptoms of schizophrenia are reduced.
  - Theory: Cognitive symptoms may result from low activity of the NMDA receptor on GABA inhibitory interneurons in the prefrontal cortex.

Genetics

1. Single nucleotide polymorphism (SNP) in genes associated with schizophrenia, notably for genes within the neuregulin-ERBB4 signalling pathway, synaptic protein genes, a potassium channel and many other brain-expressed proteins.
   a. SNPs have replicable associations with genes of major histocompatibility complex (MHC)
2. High heritability of schizophrenia is studied.
3. Common single nucleotide variations, many rare structural genomic variants, such as copy number variants and translocations, have been described in schizophrenia.
   a. Have larger causative effects than SNPs, but most are not specific to schizophrenia.

Stages

Stage 1: Risk

Features: Genetic vulnerability & environmental exposure
Diagnosis: Genetic sequence, Family history
Disability: None/mild cognitive deficit
Intervention: unknown

Stage 2: Prodrome of Schizophrenia

Features: Cognitive, behavioural and social deficits, Help-seeking
Diagnosis: SIPS, cognitive assessment, neuroimaging with addition of biomarkers
Disability: Change in school and social function (Reduced school performance)
Intervention: omega-3 polyunsaturated fatty acids, cognitive behaviour therapy, atypical antipsychotics

Stage 3: Psychosis

Features: hallucinations, delusions, disorganization of thought and behaviour, and psychomotor abnormalities
Diagnosis: Clinical interview, loss of insight
Disability: Acute loss of function, acute family distress
Intervention: Medication, psychosocial intervention

Stage 4: Chronic disability

Features: Loss of function, medical complications, incarceration
Diagnosis: Clinical interview, loss of function
Disability: Unemployment, homelessness
Intervention: Tobacco cessation, dietary management and programs to manage cardiovascular health

Pathophysiology

- Longitudinal neuroimaging studies demonstrate changes in grey matter density until the mid-twenties with the prefrontal cortex being the last to mature.
- Schizophrenic psychosis usually emerges between ages 18-25.
- Adults with schizophrenia have a history of delayed maturation including delayed developmental milestones in the first year.
- IQ is reduced early and persistently in children destined to develop schizophrenia.
- Psychosis DOES NOT emerge from a completely healthy brain.
- Structural variants associated with schizophrenia implicate neurodevelopmental genes involved with neuronal proliferation, migration, or synapse formation.
- Maternal malnutrition during famine, infections in the second trimester, perinatal injury and cytokine exposure have all been associated with subsequent increased risk for schizophrenia.
- Children with schizophrenia seem to undergo excessive losses of grey matter and cortical thinning, essentially overshooting the normal pattern described earlier for adolescents.
- 30% of children with velocardiofacial syndrome (microdeletion of chromosome) will develop a form of schizophrenia that clinically and neurocognitively cannot be distinguished from the idiopathic disorder.
- Humans - proven to be the best animal for modelling schizophrenia.
- Induced pluripotent stem cells derived from fibroblasts of patients can be useful in further study.

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