DEVELOPMENTAL MODEL OF SCHIZOPHRENIA

INTRODUCTION

- Schizophrenia is a chronic and disabling mental illness affecting millions of people worldwide.
- The study of the etiology of schizophrenia is ongoing although perspectives have changed.
- Various factors ranging from psychodynamic to autoimmune to genetic have been reported to be invoked in the causation of this disorder.

MODELS & HYPOTHESIS

- To explain the etiology of schizophrenia, various models and hypothesis have been proposed.

- These include-

1.Environmental model

2.Genetic model

3.Neurodevelopmental model

MODELS & HYPOTHESIS

4.Neuordegerative hypothesis

5.Biochemical hypothesis

6.Psychodynamic theory

7.Interpersonal theory

MODELS & HYPOTHESIS

8.Bateson & jackson model- double bind theory

9.Theodore lidz model

10.Lyman wynne model

11.Expressed emotion theory

DEFINITION

- The neurodevelopmental model of schizophrenia posits that schizophrenia results from abnormalities in development that begins in utero and continues through infancy, adolescence, and young adulthood.

WHY DO WE NEED TO KNOW THIS?

- If schizophrenia is a purely developmental disorder, then focus will be limited to understanding its etiology and refining preventive strategies.

- If a neurodegenerative element is present, then the focus will be on prevention, early intervention and treatment strategies.

HISTORY

- The proposition that schizophrenia may have its roots in early brain development dates back to Kraepelin and Bleuler

- Both have noted the neurological and behavioural abnormalities in the childhood histories of their adult patients

HISTORY

- Bender and Watt described similar abnormalities.
- But the theory that schizophrenia might be a developmental disorder was first proposed by Thomas Clouston, a lecturer in psychiatry at the University of Edinburgh.
- He called it a "developmental insanity", the last cortical developmental disease.

HISTORY

- However, Emil Kraepelin's concept of dementia praecox as a progressively deteriorating illness displaced the developmental ideas.

- In mid-1980s, Robin Murray and Shôn Lewis (Europe) and Daniel Weinberger (North America) revived the debate with new evidence supporting the ND theory.

HISTORY

- The neural abnormalities found in schizophrenia were thought to be a result of aberrant neurodevelopment.
- As this course was pursued more actively, more and more evidence supporting a neurodevelopmental theory of schizophrenia emerged.
- Evidence accumulated from various types of studies, including those of obstetric complications, facial dysmorphogenesis, genetic, neuroimaging, and neuropathological studies.

NORMAL NEURODEVELOPMENT

- It must be remembered that development is a process that occurs in the normal human brain as a function of age.

- Hence, any pathology or deviance is closely entwined with the age-associated stage of development or degeneration of the brain.

NORMAL NEURODEVELOPMENT

- There are some important facts about normal neurodevelopment:

(i) Different brain regions are generated at different times during development. Hence, the timing of the insult to the growing fetus in IU life is a major determinant of the subsequent anomaly observed.

(ii) Minor abnormalities in early events can produce large differences in subsequent stages.

NORMAL NEURODEVELOPMENT

(iii) Specific molecular signals play specific roles at various stages during neurodevelopment.

-For example, BDNF and Insulin-like growth factor (IGF) are the major signals for proliferation.

NORMAL NEURODEVELOPMENT

- Proteins such as reelin and astrotactin cause migration of the growing neurons to the appropriate positions in the brain.
- Signals from interneurons assume importance in the process of pruning that occurs in adolescence.
- All of these proteins are controlled by specific genes.

IS SCHIZOPHRENIA A NEURODEVELOPMENTAL D/O?

- Schizophrenia had also been called as a developmental encephalopathy

- Several neurological and social developmental abnormalities were also found in the children who went on to develop schizophrenia.

- Such initial observations were followed by more robust evidence.

IS SCHIZOPHRENIA A NEURODEVELOPMENTAL D/O?

- Such initial observations were followed by more robust evidence=

-Obstetric complications

-Clinical signs of aberrant neurodevelopment in the form of soft neurological signs and social and intellectual deficits

-Neuroimaging of first-episode psychosis and childhood onset schizophrenia

-Postmortem neuropathological studies

-Genes

-Developmental proteins

RISK FACTORS

A) PRENATAL & PERINATANL FACTORS

- Prenatal exposure to rubella, toxoplasmosis and herpes simplex virus type 2 are known causes of developmental disorders, including MR, learning disabilities and sensorineural dysfunction.

- Rosanoff as early as 1934 – Proposed an association of schizophrenia with complications of pregnancy and delivery.

RISK FACTORS

- Significant but small increase in risk seen in **3 categories** of obstetric complications :

1 complications of pregnancy: bleeding, placental abruption, pre-eclampsia (lowest), diabetes (highest) & Rh incompatibility

2 abnormal fetal growth and development : low birth weight (<2kg), congenital malformations, and small head circumference

3 complications of delivery : asphyxia, uterine atony, emergency CS.

RISK FACTORS

- Fetal or neonatal hypoxia considered a potential mechanism leading to ischemia & neuronal loss in temporal brain regions such as the hippocampus.

- Genetically liable individuals to schizophrenia may be vulnerable to the toxic effects of hypoxia on the developing brain.

RISK FACTORS

B) OTHER ENVIRONMENTAL HAZARDS

Maternal infections

-Individuals born in late winter or early spring have 7 -10% increased risk of developing schizophrenia later.

-This points toward an etiological agent acting during gestation, birth, or early childhood which could be secondary to exposure to maternal infections influenza

-Other intrauterine infections like rubella & herpes simplex have been suggested

RISK FACTORS

- **Maternal gestational diabetes, malnutrition**

-A study of maternal malnutrition conducted in the Netherlands also found an association of maternal malnutrition with schizophrenia.

- **Maternal stress**

-Reduce neuronal size and dendritic arborization(branching) & reductions in hippocampal volume as seen in schizophrenia

RISK FACTORS

- **Events in early childhood**

-Infants exposed to viral infections affecting CNS were five times more likely to develop schizophrenia.

-Childhood trauma, brain injury

RISK FACTORS

C) MINOR PHYSICAL ANOMALIES

- MPAs are subtle morphologic signs that are of little or no consequence but which represent fixed markers of gestational developmental abnormality.

- Morphogenesis of the brain, the craniofacial region, and epidermal ridges occur during 1st & 2nd trimesters of life from ectoderm and disturbances of development at this time can cause defects in all.

RISK FACTORS

- Different studies have found increased rates of MPAs in adults with schizophrenia.
- Similarly there is an excess of changes in the patterns and counts of epidermal ridges (also known as dermatoglyphicals) in people with schizophrenia.
- MPAs provide support for the ND model but have not yet been useful in elucidating the pathophysiology of the illness.

RISK FACTORS

- Some of the MPAs that commonly have been assessed in schizophrenia-

1. Head-

-Eyebrow abnormalities

-Fine electric hair

-Flat forehead

-Flat occiput

RISK FACTORS

2. Eyes- Antimongoloid slant, Hypertelorism, Inner epicanthic folds, Mongoloid slant

3. Ears- Asymmetrical ears, Ear protrusion, Low-set ears, Malformed ears

4. Mouth- Narrow or steepled palate, Smooth or increased palatal ridges, Tongue asymmetry, Tongue furrows

RISK FACTORS

5. Hands- Abnormal nail morphology, clinodactyly, simian crease

6. Feet- webbed toes

7. Body- Café-au-lait spots, Wide-set nipples

RISK FACTORS

D) PREMORBID FACTORS-

- Different studies demonstrated the premorbid deficits in social, neurological, and intellectual functioning in schizophrenia.

- There are evidences that people who develop schizophrenia often experience developmental deviances that are manifest in early childhood or adolescence

Studies demonstrating premorbid deficits in social, neurological, and intellectual functioning in schizophrenia

Study	Sample and F/U	Findings
British birth cohort 1946 (Jones, 1994)	5000/40 yrs	Delayed milestones, speech problems, poor social competence
David *et al*., (1997)	Swedish army conscripts 50000/12 yr	Low IQ at 18 yrs
Davidson (1999)	Israeli army conscripts 10000	IQ, social functioning, organizational ability
N. Finland cohort 1966 (Isohanni, 2003)	12000 babies/31 yrs	Delayed milestones

RISK FACTORS

- Barbara Fish observed impairments in physical, motor and cognitive development premorbidly in those who later developed schizophrenia.

RISK FACTORS

1. EARLY DEVELOPMENTAL DELAYS/ABNORMALITIES-

- There are numerous reports of developmental delays in preschizophrenic children.

- Two major British cohort studies, the National Survey of Health and Development and the National Child Development study, found delays in the speech and motor development of British children born during specified periods in 1946 and 1958, respectively

RISK FACTORS

- Motor abnormalities appear to be trait markers for schizophrenia as they have been noted in both drug-free patients and in their unaffected first-degree relatives.

- Abnormalities in schizophrenia pts and their first-degree relatives:

  -Postural
  -Upper limb motor
  -Loss of motor neuron units
  -Motor co-ordination problems

RISK FACTORS

Speech & language deficits:

- Speech and language deficits increase in frequency and severity with early onset
- Receptive language difficulties

RISK FACTORS

2. SOCIAL AND COGNITIVE DEFICITS

- **Social deficits:**

-Social isolation
-Social anxiety
-Emotional problems
-Boys being more disruptive
-Girls being more withdrawn

RISK FACTORS

- **Cognitive deficits**

  - Working memory
  -Attention
  -Executive functions
  -Speed of processing

RISK FACTORS

- Impairments in social development have been noted in a variety of studies.

- The British cohort studies- the National Survey of Health and Development, and the National Child Development study, and the Danish High Risk Study

RISK FACTORS

- **General intelligence:**

-Risk increases with decrease in IQ in schizophrenia

-Low IQ is itself a causal factor that increases the risk of schizophrenia.

RISK FACTORS

3. PREMORBID PSYCHOPATHOLOGY

- The Dunedin Multidisciplinary Health and Development Study- conducted by Kim-Cohen et al

- Found that early 53% of individuals who were diagnosed as having schizophrenia or schizophreniform disorders at age 26 years already had another psychiatric diagnosis when seen at age 15 years.

RISK FACTORS

- Studies shown that among pts having Attenuated psychotic symptom phase 40-50% becoming schizophrenia patients.

- But studies conducted in high risk patients & not in general population.

RISK FACTORS

E) NEUROIMAGING STUDIES

- Changes seen in schizophrenia-

-Increase in ventricular size of 3rd & 4th

-Cerebral cortical atrophy

-Cerebellar atrophy

-Reversed asymmetry

RISK FACTORS

-Density alteration

-Areas affected are mainly superior temporal gyrus and medial temporal lobe regions (amygdala, hippocampus, parahippocampal gyrus), insula, and anterior cingulate gyrus

RISK FACTORS

IMAGING EVIDENCES FOR ND HYPOTHESIS-

- Deficits are present in pts with first episode psychosis includes the volume of GM, hippocampus, and superior posterior temporal gyrus.

- These abnormalities present at onset cannot be explained adequately by disease progression or medication effects.

RISK FACTORS

- The normal brain is typically asymmetrical & is complete by the middle of the third trimester of gestation.
- Reduced brain asymmetry is seen in schizophrenia.
- This reduced asymmetry is likely to originate during fetal life and may be indicative of a disruption in brain lateralization during neurodevelopment.

RISK FACTORS

- Findings seen in high risk relatives of patients and also in high risk individuals exposed to IUL insults without a family history.

- Genetically predisposed individuals with developmental insults during critical periods during IUL with later significant environmental stress (life events, harmonal changes) had higher chances of findings on imaging

RISK FACTORS

F) NEUROPATHOLOGICAL & HISTOPATHOLOGICAL STUDIES-

- Neuropathological studies have confirmed imaging data (gross anatomy) but there is less consistency in histopathological findings.
- Previous studies in 1980/ 1990 showed entorhinal cortex and hippocampal neuronal disarray but could not be replicated.
- Ectopic cortical neurons and abnormal cortical cytoarchitecture were found in the prefrontal lobe in one study, which suggested abnormalities of neuronal migration.

RISK FACTORS

- Absence of classic signs of neurodegeneration in the brains of schizophrenia patients – relative absence of gliosis & necrosis argues against an adult-onset degenerative process.

- But can be explained by evidence synaptic pruning process, takes place during adolescence in humans.

RISK FACTORS

G) SUSCIPTIBLE GENES RELATED TO SCHIZOPHRENIA-

- Some of the genes that have been identified as candidate genes in schizophrenia have also been clearly shown to be linked to the process of neurodevelopment.

Gene	Function	Study
DISC-1	Neuronal migration Synaptic organization	Kamiya *et al*., 2005
		Kirkpatrick *et al*., 2006
NRG-1 (neuregulin-1)	Neuronal migration Myelination	Anton *et al*., 1997
		Traveggia *et al*., 2005
DTNBP-1 (dysbindin-1)	Synaptic plasticity	Talbot *et al*., 2004

RISK FACTORS

H) DEVELOPMENTAL PROTEINS

- Abnormalities of proteins that are specifically involved in the development of the human brain-

-Reelin -cell migration and plasticity, are found to be reduced.

-Polysialated neural cell adhesion molecule (PSA-N-CAM)- involved in axon and dendrite formation

-Brain-derived Neurotrophic Factor (BDNF)

-Glial-derived Neurotrophic Factor (GDNF)

-Epithelial Growth Factor (EGF)

CRITICS

- There is evidence of aberrations in the same process from various perspectives (etiological, genetic, histopathological, neuroanatomical, and clinical).

- This hypothesis claims that schizophrenia is a disorder of brain development.

- Hence, by definition, the disease should be early-onset *not* late-onset, untreatable *not* treatable, and static *not* progressive.

CRITICS

EVIDENCES AGAINST ND MODEL-

i) The typical age of onset for the illness is adolescence or early adulthood

ii) there is adequate evidence for late-onset cases

iii) the illness causes a marked deterioration from premorbid levels and not merely an inability to cope with peers.

CRITICS

- The hypothesis is able to address these issues by-

i) The late neurodevelopmental hypothesis explains why the disease manifests in adolescence and early adulthood.

ii) Early damage to neurons can lead to manifest pathology on interaction with normal maturational events.

iii) Premorbid abnormalities in the nervous system and behavior do exist in schizophrenia.

CRITICS

1. Delay in onset

- Why damage occurring in early life (IUL) cause psychotic symptoms decades later?

A) The early neurodevelopmental model (Weinberger)

- This is based on the view that a fixed lesion from early life interacts with normal neurodevelopment occurring later.

- Lying dormant until the brain matures sufficiently to call into operation the damaged systems.

CRITICS

- Thus, it is possible that an early developmental insult to a critical brain area, such as the hippocampus, may have delayed manifestations.

B) THE LATE ND MODEL-

- The human brain undergoes a maturational process during adolescence.

- Leads to substantial reorganization of cortical connections, involving a **programmed synaptic pruning process.**

CRITICS

- which further leads to a more efficient use of neural networks that allows the adolescent to develop increasingly complex and mature cognitive abilities.

- This model proposes that schizophrenia may result from an abnormality in periadolescent synaptic pruning (programmed elimination during development of neurons,synapses, axons & other brain structures).

CRITICS

2. EVIDENCE FOR NEURODEGENERATION

- The neurodevelopmental hypothesis cannot explain the malignant course with deterioration shown by some patients over time & also the mild progression of structural abnormalities on imaging seen in patients.

- Absence of gliosis and of any other histological evidence of degeneration such as inclusion bodies, is the strongest argument against neurodegeneration.

- It can be explained by the abnormal pruning/ cell death by apoptosis (glutamate exicitotoxicity) leading to volumetric reductions of the brain

CRITICS

3. OTHR EVIDENCE-

- Precipitating factors- Social risk factors, Infections, adverse life events, stress etc

- NT (Dopamine, Serotonin, GABA, glutamate, NMDA Receptor hypofunction)abnormalities

CRITICS

NT ABNORMALITIES-

- DOPAMINE HYPOTHESIS-

-symptoms of Schizophrenia result from overactivity of dopamine system, specifically the D2 receptor

EVIDENCE-

-Many effective *neuroleptic* (antipsychotic) drugs block dopamine receptors → *reduces* activity of dopamine

-L-dopa treats Parkinson's disease by *increasing* dopamine activity → sometimes produces Schizophrenia-like symptoms

CRITICS

- Shitij Kapur (2003, 2005) proposed that-

- A dysregulated, hyperdopaminergic state, at a "brain" level of description and analysis, leads to an aberrant assignment of salience to the elements of one's experience, at a "mind" level.

- Acute psychosis is “a disorder of dopamine-induced aberrant salience”

CRITICS

- Under normal circumstances, a stimulus-bound release of dopamine mediates the attribution of emotional relevance or salience to stimuli which is reflected in appropriate thoughts and behaviors.

- In acute psychosis there is an exaggerated dopamine transmission, out of synchrony with any stimuli/ dopamine dysregulation which leads to the assignment of inappropriate emotional and motivational relevance to external and internal stimuli.

- This aberrant attribution of salience is perpetuated in the absence of any further stimulus, since it is generated by abnormal neurochemistry.

CRITICS

- **NMDA receptor hypofunction** is a theory proposed on the basis of the observation that antagonism of NMDA receptors with drugs like ketamine causes psychotic symptoms.

- GABA interneuron-GABA have regulatory effect on dopamine activity & loss of GABAergic neurons could lead to the hyperactivity of dopaminergic neurons.

- Role of serotonin- Serotonergic neurons have modulatory effect on dopaminergic neurons

CRITICS

GLUTAMATE-

- It has been postulated that glutamate could be the link between neurodevelopment and neurodegeneration
- It plays a role in several stages of neurodevelopment (neuronal migration, survival, and plasticity).
- In adolescence it is involved in plasticity and pruning
- In old age it is involved in neurodegeneration through excitotoxicity.

CRITICS

- EVIDENCE-

-Phencyclidine(PCP), a glutamate antagonist in acute ingestion causes symptoms like positive & negative symptoms of schizophrenia.

-Chronic PCP intake produces a hypodopaminergic state in the prefrontal cortex & prduces negative symptoms.

CURRENT HYPOTHESIS

INTEGRATED MODEL OF SCHIZOPHRENIA

- In this model, the neurodevelopmental model is extended to, and combined with, sociodevelopmental, cognitive, neurobiological, G × E, and epigenetic hypotheses.

- Epigenetic hypothesis suggests that the onset of schizophrenia is influenced not only by the additive or interactive action of static gene and environmental factors but also via epigenetic dysregulation of gene activity.

CURRENT HYPOTHESIS

PROGRESSIVE NEURODEVELOPMENTAL HYPOTHESIS

- This term and concept is new
- It includes both neurodevelopmental & neurodegenerative hypothesis.
- Its biggest strength is that the theory emerges from research findings.

CONCLUSION

- Schizophrenia is a complex and unique disorder and probably cannot be explained by a single process of development or degeneration.
- Research evidence exists for degeneration as well as development, although at present, evidence for the latter appears to be stronger.
- Finally, it should be remembered that viewing schizophrenia as having both components of development and degeneration is therapeutically more optimistic.

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THANK YOU