Tracking Genetic And Biological Basis Of Schizophrenia

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Abstract

Schizophrenia is a multifactor disorder of mind with a constant prevalence of 1-2% in the population. It causes not only significant physical morbidity and social incompatibility to the patients, but also invites major economic hardship for its lengthy diagnostic procedure, devastating course, frequent treatment failures and very difficult rehabilitation measures. Such a debilitating picture of schizophrenia has made it an enticing research topic in psychiatry. The origin of schizophrenia stands on the orchestrated effect of various aetiologies, e.g. genetic, anatomical, physiological, social, psychological, interpersonal, and many others. It is extremely difficult to evaluate individual aetiologies at the backdrop of schizophrenia as these are tightly intertwined. The present review is interested to highlight the two basic-tiers: A) genetic predisposition, and B) other biological stressors behind the onset of schizophrenia. It first critically analyses how each tier contributes to the development of the illness. Next, it hypothesizes a possible link among them at the back drop of the emergence of schizophrenia. Finally the paper proposes future researches.

INTRODUCTION

For past three decades, schizophrenia-researches were mostly epidemiological, biological or therapeutic. Researchers probably did not get much scope to work beyond these boundaries due to I) tremendous diversities within the area itself, II) lack of motivation and scope for interdisciplinary research, III) scarcity of necessary infrastructure to do a large multicentric interactive research, III) sub optimal patient participation due to social taboo related to psychiatric illnesses, and IV) lack of integrity of the data among major psychiatric centers across the world.

The origin of schizophrenia has got so many postulations, e.g. anatomical, genetic, interpersonal, biological, social, psychological, environmental or epidemiological, but no fruitful attempt has been made to intertwine these aetiological factors to propose a concrete hypothesis related to its occurrence in the susceptible population.

The present paper has meticulously reviewed the related literature in MEDLINE, Medscape, PubMed, and PsychInfo for proposing A. hypothesis in an interactive model to explain how gene and other biological factors play crucial roles together behind the development of schizophrenia in the population and B. how a database can be prepared for gaining more detail information related to the onset, course, treatment response, trend and prognosis of schizophrenia in a particular population.

The following section of the article ties to provide an overall view regarding the aetiopathogenesis of schizophrenia.

SECTION A. UNDERSTANDING THE DISEASE PATHOGENESIS

This section briefs how schizophrenia-susceptibility develops at birth and later full blown schizophrenia is evolved in the population by the modulating effects of the biological factors:

TIER ONE

GENE AND SCHIZOPHRENIA

Human Genome Project has discovered several genetic linkages behind the origin, pathogenesis and even prognosis of a disease. Schizophrenia is of no exception! Genetic factors are proposed to be responsible for the familial predisposition of schizophrenia (more than 80%) [1]. Epidemiological data showing chance of its development in the population is as follows: a) around 47% in monozygotic co twins (highest concordance), approximately 6.6% when the disease is prevalent among first-degree relatives[2], and possibility of developing schizophrenia in the offspring is approximately 25-50% when the mother is schizophrenic[3]. These strongly support the genetic basis of the illness. Recently genetic linkage studies have shown that chromosomes 1, 2, 4-11, 13, 15, 18, 22 and X have vulnerable loci for schizophrenia[4]. Few of these recently

discovered linkages are documented as follows:

Figure 1

Table 1

Author	Susceptible Genetic-linkage
Semwal et al, (2002)[5]	Promoter region of the ***serotonin 2A receptor gene*** and ***tryptophan hydroxylase gene***.
Liu et al, (2002)[8]	***22q11 microdeletions*** (the highest known genetic risk factor, second only to that of the monozygotic co twin).
Meloni et al, (2002)[10]	The ***microsatellite HUMTH01***, in the first intron of the Tyrosine Hydroxylase (TH) gene (encoding the rate-limiting enzyme of catecholamine synthesis).
Ben-Shachar, (2002)[9]	***Mitochondrial-gene***-impairment (e.g. altered cerebral energy metabolism, mitochondrial hypoplasia, dysfunction of the oxidative phosphorylation system and altered mitochondrial related gene expressions) behind the diversified clinical and pathological picture of schizophrenia. Secondly, the interaction between "dopamine" and "mitochondrial respiration" is considered to be one of the possible underlying mechanisms behind the hypo or hyper dopaminergic activities at the backdrop of schizophrenia.
Saito et al, (2003)[6]	***PIK4CA maps to 22q11*** regions.
Gasperoni et al, (2003)[7]	A region on the ***distal portion of chromosome 1***.

This is untrue that genetic linkages are 'mandatory' behind the onset of schizophrenia. Interestingly schizophrenia can also occur without parental or sibling history of the illness! [11]. Therefore, it is anticipated that gene could be responsible for triggering the necessary 'susceptibility' or 'vulnerability' of schizophrenia in a population, but it is not the 'all' for the emergence of the illness. Genetic effects need to be catalyzed further by several other factors and so the article now reviews the biological factors those may facilitate the gene-induced-evolution of the illness as follows. Environmental, social, interpersonal and other causative factors behind the onset of schizophrenia are also useful clues but are beyond the scope of the present article.

TIER TWO

OTHER BIOLOGICAL FACTORS AND SCHIZOPHRENIA

Apart from genetic susceptibilities, other biological factors also start playing as early as one's birth. Birth-related complications of several types often lead to 'early cerebral insult' in the genetically at risk babies[12]. Moreover, studies have also observed that babies, later on turned into schizophrenics, sustain more birth related complications too[13]. So, there are direct and indirect proofs that obstetrical complications possibly play a major role in the development of schizophrenia in the population.

Birth related complications are various: 1. Maternal influenza during winter-spring could be critical for the foetal brain as influenza virus are neurotropic in nature[14], 2. Birth order, especially higher the birth order higher the risk[15], 3. Multiparity[16], 4. Bleeding in pregnancy[16], 5. Rh-isoimmunization[17], 6. Antenatal exposure to toxins[18] and drugs[19], 7. Maternal illness e.g. diabetes mellitus[16], thyroid disorders[20] and many others. Most of the above-mentioned maternal complications do not have any direct proof why these are schizophrenogenic in the babies. These are all evidence-based epidemiological studies whose biological bases are largely debated.

Foetal complications like, small for gestational age babies[21], low-birth-weight babies[21], preterm babies[21], babies having small head circumference[22] and minor physical anomalies[23], and babies, who have sustained birth asphyxia due to several reasons [24] may predispose an early cerebral insult. These further lead to some structural and functional changes in their brain and such pathological changes possibly push them into a schizophrenia-prone future. Another interesting finding is that schizophrenic mothers are prone to develop several complications during their pregnancy period and childbirth[26]further adding to the population of schizophrenia-prone babies setting a vicious cycle. The biological bases of such observation are still not very convincing.

The role of caeserian section on fetal brain is questionable, because animal studies (rat) have shown that caeserian-borne mice have a tendency to have enlarged cerebral ventricles (often found in schizophrenics) with the loss of stress-reactions (no or very low response with tail pinching those mimic catatonia) than those who are borne by vaginal delivery[25]. These findings need extensive study on caeserian-borne human babies to find out some acceptable correlation (clinical and anatomical) with the emergence of schizophrenia in human population.

Apart from birth complication-induced-cerebral-damage, it is also evident that neurological disorders in the children, e.g. epilepsy[3], childhood cerebral infections[3], and anomalous changes in the brain[27] etc. are also directly or indirectly related to the onset of the illness.

Therefore it is hypothesized that 'preprogrammed susceptible genes' might have made the cerebral neurons more vulnerable and fragile under the overwhelming influence of cerebral hypoxia prior, during or after birth. A trace of such neuronal vulnerabilities keep persisting throughout one's life and probably pushes the susceptible person in the vortex of schizophrenia. Again this hypothesis needs further researches.

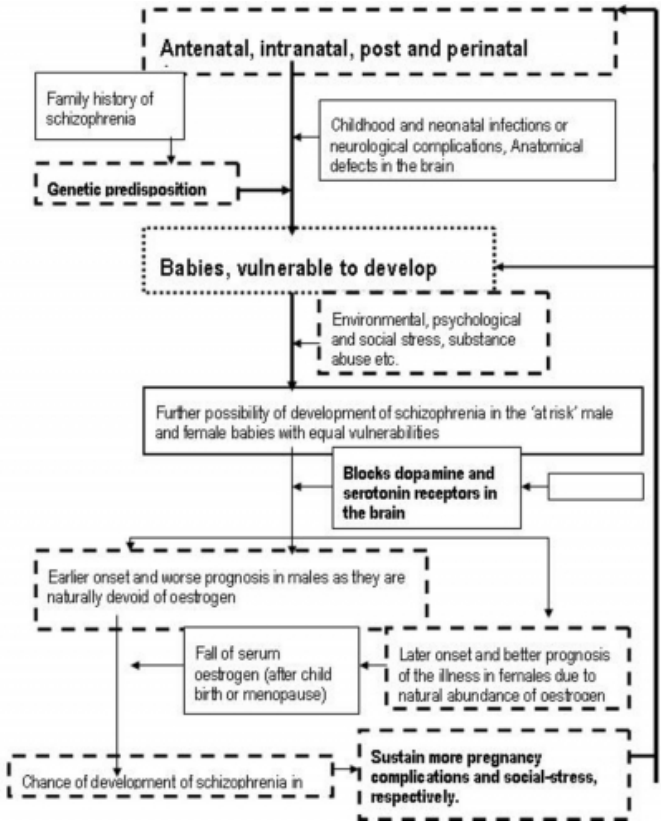
A large body of studies has shown that young males are the principal victim of schizophrenia compared to young females[28], though contrasting studies exist. Therefore the present article is curious to explore despite of equal genetic predisposition and biological adversities why males develop schizophrenia earlier and suffer worse than females. A crux of research has been made for finding out the possible causes. Among these the role of oestrogen is largely studied and a chunk of data has substantiated that oestrogen possibly acts as a biological neuroleptic in females preventing them form schizophrenia[29]. By blocking the dopamine[30] and serotonin[31] receptors in the brain, like many antipsychotic drugs e.g. haloperidol (blocks dopamine receptors, especially D_2) and risperidone (blocks D_2 and 5-HT_2). That's why females develop the illness probably later when they lose oestrogen naturally[32]. In fact females show tendency to develop schizophrenia after childbirth[33] or menopause[34] when serum oestrogen level is certainly low. Thus it is postulated that oestrogen may be an important factor behind the male-female heterogeneity in schizophrenia but requires further extensive research at the neuromolecular level for establishing the roles of oestrogen in the brain.

As presumed, genetic load and biological stressors trigger the development of schizophrenia in addition to other human factors e.g. immigration[35], urban-birth and upbringing[36], quality of life[37], substance abuse[38], cultural and ethnic status[39], childhood traumatic experiences[40] and many more. The tentative reason behind such an apprehension is that these factors are essentially intrigued with one's biological life. These manipulate one's mental faculty physiologically and psychologically and moreover, a schizophrenic's brain is extremely hypersensitive to any form of stress[41]. Therefore, anything that generates stress of any form may trigger the process to be 'on' in a schizophrenic brain.

After careful display of the genetic and other biological factors behind the onset of schizophrenia, the article links the major components, derived from each tier and proposes a self-explanatory model regarding the origin of schizophrenia in the population.

Figure 2

Model 1: The origin of schizophrenia (gene-biological basis)



CONCLUSION

Susceptibility for developing schizophrenia is as early as from one's birth. Schizophrenia is considered to be an inherent "nervous system fragility in the brain"[42]. It is postulated that this inherent neuronal 'fragility' in the brain could be genetically pre programmed (may be from the time of conception). Such 'fragility' possibly makes the brain tissue extremely vulnerable to any degree of oxygen deprivation during antepartal, intrapartal or postpartal complications or due to childhood neurological problems. The vulnerable brain grows as the babies grow and further, during its lifetime, different adverse situations transform the risk to reality. Young males are worse sufferers than young females probably they are lack of antipsychotic-like effects of oestrogen in the female brain. Though these are extremely premature assumptions, yet there are scopes for the necessary testing of the hypotheses.

FUTURE RESEARCH PROPOSALS

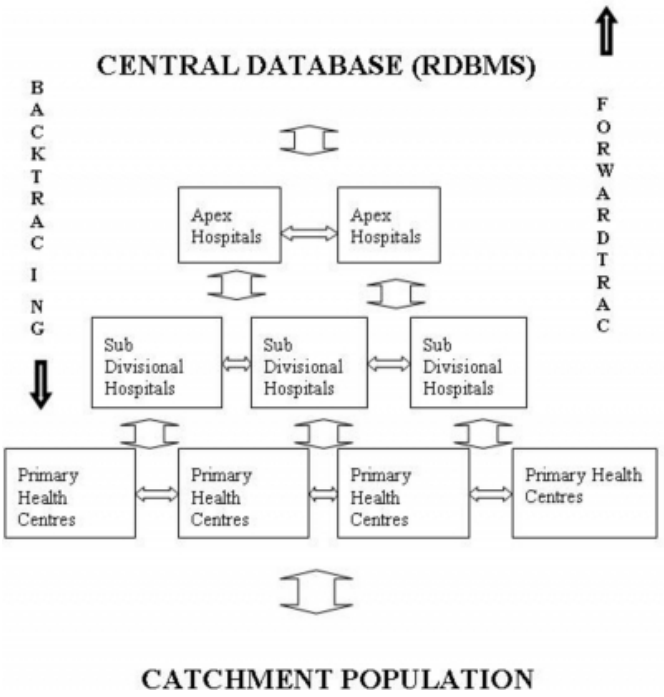
Understanding the genetic basis of schizophrenia is still in its infancy. The meaning of health specifically highlights a continuously synchronized interplay of billions of protein

molecules at the optimum time, rate and place. These functional proteins are the production of genes. Alteration of gene is called mutation that can be taken place due to several reasons. Commonest of these is single changed base in the DNA, a misspelling. Remaining causes of mutation could be due to the loss or gain of a base in a DNA segment, or sometimes long segments of DNA can be multiplied or missing. Some mutations are silent and neither the structure nor the functions of the encoded protein are critically affected. Other mutations result in an altered protein. Schizophrenia probably also follows the same basics of genetics for the generation of its susceptibility to its development in a person although the overall process may be extremely complex and yet to be known in detail. Moreover, it is untrue that genetic susceptibility always gets transformed to the full-blown schizophrenia. Therefore, it would be interesting to search what are the key factors those convert the ‘susceptible' gene to the ‘disease' gene and how.

Regarding the record keeping is concerned, in the third world courtiers due to huge patient load at par to the high degree of population it is often very shabby. Therefore the second future research proposal is to develop a database incorporating patient's records for easy tracking of the patients. The scheme is shown below:

Figure 3

Model 2



Flow of data across hospitals to track the affected population either from birth-to-disease and vice-versa.

EXPLANATION OF THE MODEL

The model proposes the skeleton of the epidemiological research for forward and backward tracking of the schizophrenic population. Forward tracking means following the vulnerable babies (who are having family history, sustained birth-asphyxia or related neurological problems) to see whether they have developed schizophrenia or not. While the backward tracking means whether schizophrenic population had any family history, birth related complications or childhood neurological problems. The article also proposes that with such approaches the relatives of the patients can also be traced following the family tree.

Record keeping and its flow across the hospitals should begin with the primary health centres to sub divisional health centres and then to the apex centres and vice versa so that hospitals of any sector can access, add, and maintain the overall database which in turn may be accessible by the researchers of the different institutes. Deletion of a record from the database needs to be approved by an apex committee to avoid data loss. This approach may be welcome to ease the future multidisciplinary research on multifaceted illnesses like schizophrenia for a better understanding of its basis. Proper maintenance of the database can also dilate the data-access strictures, which are the greatest hardships in a multidisciplinary research.

POSSIBLE HARDSHIPS OF THE MODEL

1. Requires a huge manpower (database administrators, data entry operators, server and instrumental maintenance and so on),
2. Motivate the concerned medical and paramedical persons to enter the revalidated data related to the history of one's birth, childhood, adulthood and old age-related neuropsychiatry problems,
3. Making the data entry process in the hospitals (primary, secondary and tertiary sectors) mandatory,
4. Extremely lengthy process of data entry,
5. Providing the required authentication numbers to the users for research purpose,
6. Maintaining the huge database could be very costly, and
7. Strict maintenance of confidentiality of patient's medical records.

BENEFITS OF THE MODEL

1. Thorough epidemiological studies could be done easily due to easy access of patient record from its birth,
2. Trend of schizophrenia can be detected in a certain population,
3. Many other genetic diseases related to psychiatry can be studied in the same database with some advance formatting according to the needs, and
4. Interlinking schizophrenia with the related illnesses could be possible.

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