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Review Article

The Autoimmune and Infectious Etiological Factors of a Subset of Schizophrenia

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Abstract

Despite progress in neurotransmitter identifications and the emergence of novel antipsychotics, the treatment of schizophrenia remains frustrating. There is now a flurry of research trying to figure out the aetiology of schizophrenia and potential etiological models other than neurotransmitter dysfunction deserve consideration. Recent years have witnessed a revival of interest in the viral and immunity based etiological models of schizophrenia. . A subset of schizophrenia may have a pure biological aetiology. There are several commonalities between schizophrenia and autoimmune disorders. Coexistence of established autoimmune disorders along with schizophrenia is suggestive that the latter could also have an autoimmune component. Antipsychotics may be working on the principle of immune modulatory and neuro- modulatory mechanisms. The well recognized 1% global consistency of the incidence of schizophrenia indicates that the aetiology of schizophrenia involve an evolutionary genetic vulnerability and universally present environmental factors. There may be a genetic predisposition to the hypothetical "schizovirus" determining the development of schizophrenia in certain individuals. Certain people are genetically vulnerable to microbial infections in the sense that they have a highly sensitive surveillance system to the microbial infection and respond to the microbial adversary in an exaggerated way. Such a vulnerability and anomalous reaction to infection could result in the schizophrenia psycho-pathogenesis.

Keywords: schizophrenia, autoimmune disorders, schizovirus, genetic vulnerability

Introduction

A clearer understanding of the aetio-pathogenesis of schizophrenia would ultimately lead to effective treatment strategies and provide the impetus for elucidation. The autoimmune hypothesis promulgates that it is the auto-antibodies that are responsible for schizophrenia and, according to the viral hypothesis, it may be the body's abnormal response to a slow viral infection or the undefeated viral antigens causing the schizophrenia pathology. The autoimmune and viral hypotheses are interlinked, as autoimmune disorders can be triggered by microbial infection. Viral aetiology is less convincing than the autoimmune model, but from a treatment perspective, the former is more promising than the latter. To gain a detailed understanding of aetiological models of a subset of schizophrenia, herein the author has reported on a review of the literature relating to the immunity- and viral-based aetiological models of schizophrenia. Genetic vulnerability has been highlighted in the schizophrenia literature alongside environmental factors. The veracity and contestability of the immunity- and viral-based aetiological hypothesis of schizophrenia merits further investigation.

Schizophrenic Syndromes

A prerequisite for incorporating autoimmune and viral aetiology into a scientific discussion would be acceptance of the heterogeneous hypothesis of schizophrenias; they may be a cluster of entities with different aetiologies and the end-stage of different disease processes.[1] Autoimmune or viral aetiology may account for one subgroup.

Schizophrenia has diverse signs and symptoms, and a long history of controversy. Nosologists designate it as polythetic, whereas most other mental illnesses are monothetic, seemingly affecting only one brain system.[2] In the second half of the twentieth century, the psychosocial model gave way to evidence that it is a brain disorder. Schizophrenia has a long history of controversies and there has been much contention over the aetiology, psychopathology, nomenclature, and diagnostic criteria. Schizophrenia is currently seen as a neurodevelopmental encephalopathy, in which the cognitive deficits are produced due to the errors during the normal development of the brain[3] or a neuro-degenerative disorder and the cognitive deficits are derived from a degenerative process that goes on unalterably. Modern neuroimaging techniques and an intensification of studies of necropsy tissue have been responsible for this shift. Researchers seem to agree that a neurodevelopmental or degenerative assault precedes the symptoms by several decades.

The aetiology of the cognitive deficits is unidentified and several potential factors, genetic and epigenetic, are envisaged. Environmental factors—including infectious agents and disturbance in utero through malnutrition—account for a few cases. Autoimmunity and viral theories would fit in with the neuro-developmental and neurodegenerative hypotheses. Proponents of viral aetiology view viruses as acting alongside

susceptible genes to initiate a trajectory that manifests as psychotic symptoms.

Lessons from Autoimmunity

Disorders of an autoimmune nature are known to occur with increasing frequency in patients with another autoimmune disease. This is somewhat like the coexistence of multiple psychosomatic disorders in a person; as per Halliday's psychosomatic formula, association of other psychosomatic afflictions justifies the diagnosis of a new psychosomatic condition. [4] It is well recognised that the central nervous system (CNS) may be directly affected by autoimmune processes, as in the case of multiple sclerosis (MS) and autoimmune limbic encephalitis. A physical autoimmune disease, such as systemic lupus erythematosus (SLE) and antiphospholipid syndrome are also associated with psychiatric morbidity. Paediatric autoimmune neuropsychiatry disorder is a post-infection (group A Beta-haemolytic streptococcal infection) autoimmune disorder characterised by abrupt onset of obsessive compulsive disorder (OCD) and Tourette's syndrome, brought about by molecular mimicry. [5] Nicholson et al observed that 20% of OCD patients were positive for anti-basal antibodies, considered to be part of a post-streptococcal autoimmune reaction. [6]

Autoimmunity is a misdirected response occurring when the immune system attacks the body; it is the loss of tolerance to self-antigens. Immunological tolerance to one's own tissue is probably normally acquired during foetal life, helping to prevent the occurrence of the autoimmune process (see Table1). Some clones of cells that can produce auto-antibodies (forbidden clones) are thought to be produced throughout life, and are suppressed by large amounts of self-antigens or antigen-specific T cells. Auto-antibodies are produced for a wide variety of antigens; some are organ-specific and others are non-organ-specific. Some microorganisms or drugs may trigger changes in individuals who are genetically vulnerable to autoimmunity.

A human disease may be considered of autoimmune origin on the basis of knowledge from molecular biology and hybridoma technology, [7] along with the Witebsky postulations. It is established by the presence of auto-antibodies and T cells that react with host antigens. Approximately 25% of patients with an autoimmune disease (AD) tend to build up additional auto-antibodies. Strausburg et al (1996) explained several hypotheses for the virally-triggered autoimmune mechanism (see Table 2). [8] Allergy is the consequence of a strong response to a harmless substance, but ADs are caused when the destructive potential of the immune system is misdirected to oneself. ADs share common effect or mechanisms with hypersensitivity reactions and can be classified into three main types corresponding to the type ii, type iii, and type IV categories of hypersensitivity reactions (see Table 3)

Table 1- Mechanisms preventing and causing autoimmunity

Tolerance to self molecules a. Clonal deletion-removing any lymphocytes that might react to self molecules b. Clonal anergy-decreasing the responsiveness of lymphocytes that recognise self-molecules. c. Receptor editing-rearrangement of B-cell receptors. d. Reduction or inhibition of molecules or antigens that may cause self recognition. Failure of self tolerance a. Release of isolated auto antigens-tissue trauma or infection may cause breakdown of anatomic barriers and may expose the hidden antigens for recognition of T cells that were not deleted during development. b. Structural alterations in self peptides- Once structurally altered by a trigger such as infection , the self-peptides become more antigenic and are subsequently recognised by the undetected T-cells evoking immune response. c. Molecular mimicry-based on a structural similarity between a pathogen or metabolite and self structures, evoking an immune response against the foreign particles but also an autoimmune response against the self molecules they resemble. d. Polyclonal activation-Infectious agents activate our immune system, B cells and T cells are stimulated resulting in abnormal production of immunoglobulin specific for self molecules. e. Genetic predisposition

Table 2 - Virally triggered autoimmune mechanisms

a. Molecular mimicry -a protein or polysaccharide on the virus may be structurally homologous to a host molecule and the immune system being unable to differentiate between the two, may then cross react with host cells and tissues expressing this molecule. b. The virus may cause release into the circulation of auto antigens that are normally hidden from the immune system. c. The virus might pick up host proteins from the cell membranes that become immunogenetic since they are present on the virus particle. d. The virus in the process of replication may structurally change the host proteins that in turn become recognized as foreign to the immune system.

Table 3 - Classification of Autoimmune disorders

Type i-no autoimmune diseases are caused by lgE, the source of type i hypersensitivity reactions. Type ii-caused by antibodies directed against components of cell surfaces or the extracellular matrix Type iii-caused by soluble immune complexes deposited in tissues Type iv- caused by effector T cells.

Shared Aetiology

ADs are characterised by shared threads in terms of their propensity to co-exist in a patient or direct relatives. Two major autoimmune clusters have been recognised via, thyrogastric—mostly organ-specific—diseases and lupus-associated—mainly multi systems—diseases. [9] Some ADs are distributed within either cluster and there are also overlaps within each cluster. These patterns of concurrence depend predominantly on genetic determinants.

Poly-autoimmunity is the term proposed for the association of multiple autoimmune disorders in a single patient and such co-occurrences indicate a common origin of the disease. [10] Adriana et al, by grouping diverse ADs in the same patient, demonstrated that they are true associations as part of autoimmune tautology rather than chance findings.

Co-Occurrence of ADs

Theories for autoimmune aspects of schizophrenia raise the concept of early infection by microorganisms with antigens so analogous to CNS tissue that resulting antibodies act against the brain. Some data suggest that an autoimmune process precedes schizophrenia, non-affective psychosis, and bipolar disorder, [11] but do not establish whether this is affected by viral attack, as viral footprints may be hard to detect, especially in the target organ, once the autoimmune process has begun. Psychosis is reported in 25% of SLE cases.

A Danish study revealed that schizophrenia is associated with a large range of ADs. [12] The researchers found that a history of any AD in the patient is allied with a 45% increase in the incidence of schizophrenia. Specifically, nine ADs have a higher prevalence rate among patients and 12 ADs have a higher prevalence rate among their parents than among comparison groups. In comparison with the control group, Thyrotoxicosis, Celiac disease, Acquired haemolytic anaemia, interstitial cystitis, and Sjogren's syndrome had a higher prevalence rate among schizophrenia sufferers and their family members.

Three of the Ads—namely, celiac disease, thyrotoxicosis, and acquired haemolytic anaemia—have been previously associated with schizophrenia. Celiac disease involves an immune reaction to wheat gluten. This could be due to increased permeability of the intestine, raising the level of antigen exposure, resulting in increased risk of an autoimmune response to brain components or it may be that gluten proteins are broken down into psychoactive peptides. Eaton et al opined that the association of schizophrenia and ADs could be due to common genetic causes, perhaps related to the HLA or other genes, and some cases of schizophrenia may be consequential to the production of autoantibodies that disrupt the brain function.

Researchers for a Taiwan study identified a greater variety of ADs in schizophrenic patients than anticipated and recommended further research. [13] Chen *et al.* found that 15 ADs are significantly associated with the schizophrenia group. Their studies also confirmed an earlier observation of a negative relationship between schizophrenia and rheumatoid arthritis (RA). It has been observed in a small sample study that mothers of schizophrenia patients have a lower risk for RA.[14]

Rheumatoid Connection

The negative correlation between schizophrenia and RA is puzzling. [15] Such dissociation was interpreted as the effect of antipsychotic medication. Similarly, the metabolic changes associated with one disease may inhibit another.[16] Genes predisposing a person to have one disorder may have a protective influence against another and, in that way, the negative rheumatoid connection with schizophrenia is consistent with an autoimmune model.

RA has a genetic predisposition partly mediated by major histocompatibility complex (MHC) alleles and triggered by infection. Similarly, schizophrenia has genetic and environmental associations and has been cautiously connected with MHC genes other than those perhaps involved in RA. In addition to gene products accountable for antigen presentation, the MHC gene complex holds a multitude of genes-controlling aspects of immune response. Hypothetically, depending on the set of genes an individual has inherited at the MHC complex, a viral assault will lead the immune system to an immune cascade toward the development of RA, or along a genetically-predetermined path with a network of cytokines and immune mediators and directed against CNS components, resulting in schizophrenia. [17]

The negative rheumatoid connection may be attributable to two mutually-exclusive alleles of the same gene. Such associations may lead to novel treatment strategies; sickle cell anaemia patients are thought to be less affected by malaria. Of note, the combined research of Karolinska Institute in Sweden and John Hopkins's University School of Medicine in the United States have recently discovered the genes and the specific deoxyribonucleic acid (DNA) sequences that regulate them plot together to the progress of RA; rheumatology may be inching close to an early detection method and effective treatments. Such a development could hopefully happen in the schizophrenia research.

Commonalities

Even though ADs superficially seem different, the vast majority of them share several similarities. Like ADs, schizophrenia, as such, is neither infectious nor congenital. Schizophrenia and ADs have well-established genetic propensities, and a combination of genes, rather than a single gene, is thought to be responsible for their manifestations. Both schizophrenia and ADs can be triggered by environmental toxins and they have a remitting and relapsing course. Worsening of symptoms is observed when patients are exposed to stress and both conditions have a peak increase in late adolescence or early adulthood. These similarities argue in favour of an autoimmune aetiological model of schizophrenia. [18]

Apparently, there is an interesting epidemiological dissimilarity between ADs and schizophrenia. The incidence of ADs is on the increase in developed countries, whereas schizophrenia has a consistent incidence of 1% globally. According to the hygiene hypothesis of ADs, the widespread practice of hygiene, vaccination, and antibiotic therapy in rich countries have disabled children's immune systems to deal with proper infections and are more geared to charge with one's own tissues in highly-destructive ways. [19] The incidence between the sexes was thought to be almost similar in the case of schizophrenia, but a recent study shows that for every three males with schizophrenia, there are two females with the disease. [20] ADs are slightly higher among the female population.

Immune Modulation of Clozapine

Antipsychotics may have an immunosuppressant effect; plasma levels of IL-6, soluble IL-6R and transferrin-receptor (TfR) were significantly lower after antipsychotic drug treatment. Activation of cell-mediated immunity may occur in schizophrenia; neuroleptic agents may modulate this through suppression of IL-6 or IL-6R-related mechanisms. [21] The antipsychotic effect may involve a counter-effect on the brain-mediated immune system.

Clozapine, the gold standard for refractory schizophrenia, is a dibenzodiazepine and lowers D2 receptor occupancy and is also a 5-hydroxytryptamine antagonist. Studies indicate that among the atypical antipsychotics, clozapine seems to have an immunosuppressant effect along with neuro-modulatory effect. It has been suggested that clozapine may diminish antibody synthesis in hematopoietic cells and also argued that a possible immunosuppressive action may contribute to its superior antipsychotic efficacy. [22] The long-term immunosuppressive effects of antipsychotics may inhibit putative autoimmune responses against neurological sites and could, thus, act synergistically with the direct antagonistic action on brain receptors for the evident improvement of psychotic symptoms. [23] It is also conjectured that the increase of soluble IL-2 receptor levels in Clozapine-treated patients indicates an immunosuppressant mechanism. [24]

Haloperidol may also be a neuro-immune-modulating drug. A study of in-vitro effects of clozapine and haloperidol on cytokine production by human whole blood suggested that both drugs, at concentrations within their therapeutic range, may exert immunosuppressive effects through an enhanced production of IL-1 receptor antagonists. [25]

It is well recognised that unlike other antipsychotics, clozapine works better over time, as immune modulation may take longer than neuro modulation. In addition to the neuro modulation, antipsychotics may be working on the principles of immune modulation, as well. If a derivative of clozapine, without its haematological and metabolic side effects is discovered, such a drug would become the first line of choice among the antipsychotics, and that could be a significant event in schizophrenia research. The immunosuppressant effects of clozapine seem to have public health awareness that patients on clozapine are advised to have the winter flue jab. Elderly patients on antipsychotic medications are more prone to get pulmonary infections, indicating that such drugs have a delicate immunosuppressant property.

Autoimmune-Neuropsychiatric Disorder?

If schizophrenia is an AD, a higher rate of other ADs may be expected among schizophrenics. Most studies confirm that it is tied to irregularities affecting multiple levels of the immune axis.There are multiple interlinked causative factors in the aetiology of schizophrenia. There are suggestions that the neuro-behavioural changes follow an abnormal response to microbial invasion, but that does not necessarily lead to an autoimmune process. The literature deciphering the role of viruses in neurotransmitter abnormalities linking neurodevelopment assaults and the neuropsychological manifestations of schizophrenia is unhelpful. For those who adhere to the autoimmune model of schizophrenia, the simplest suggestion would be that the pathogenesis of the subset of schizophrenia studied may be caused by antibodies in the plasma and CSF that react with brain proteins, resulting in a neuro-autoimmune process.

Lessons from Viral Infections

The concept that certain psychiatric disorders are the neuro-behavioural sequel of the body's immune response to viral infections was prevalent in the early part of the 20th century. That was an outcome of research conducted into rabies in the late 1880s, which revealed the affinity of viruses for the nervous system. Research into tertiary syphilis also provided evidence of an infectious aetiology for specific psychiatric disorders. Investigation of the encephalitis lethargica pandemic (1919 - 1928) contributed to recognition of viral causation on account of similarities apparent between the psychotic symptoms associated with encephalitis lethargica and the clinical presentation of schizophrenia. [26]

Post-influenza depression, depression following mononucleosis, and hallucination associated with herpes encephalitis are well recognised. Menninger, who studied post-influenza psychosis, promulgated the first acceptable viral hypothesis for schizophrenia. [27] In the mid-twentieth century, psychodynamic studies began to encompass the origins of schizophrenia and viral aetiology lost its novelty. Dementias associated with Acquired Immune Deficiency Syndrome (AIDS) have reawakened interest in the correlation between virology and psychiatric disorders, and different authors have revisited these hypotheses in the last three decades. [28-36]

The immune response to influenza and other viruses involves cell-mediated immunity and cytokine activity, which tend to turn tryptophan into kynurenic instead of serotonin. The outcome of this deviation is mood disturbance. It is the body's immune response that blocks the conversion of tryptophan into serotonin, thereby resulting in post-influenza depression. It is

arguable that there may be other psychiatric disorders consequential to a slow immune response of the body to viral infections. The possibility of viral oncogenesis was originally ridiculed, but now there is some evidence to support the view that viruses are responsible, at some stage, for approximately 20% of human malignant diseases. [31]

In theory, a virus could induce schizophrenic symptoms or depression by stimulating antibodies that cross-react with brain tissue, without necessarily gaining entry into the brain. At different developmental stages, the immune response may become less efficient and viral agents may become potentiated, leading to neuropsychiatric conditions. The supposedly inflammation-mediated brain diseases occur at different stages—for instance, schizophrenia in late adolescence or early adulthood, and Alzheimer's typically at an advanced age. It is well established that the human immunodeficiency virus (HIV) may lead to a form of AIDS dementia, and other common viruses that infiltrate the neurons may cause other types of dementia. HIV/AIDS and Borna Disease Virus (BDV) in animals help to bring the infection-based model of schizophrenia to the realm of scientific imagination

Viruses can influence the human genome. After becoming effective, viral sequences are integrated into the genome of brain cells. These sequences are not thought to be inheritable, but may cause mutations that interfere with brain functions and contribute to the development of psychiatric disorders. [37] It may be arguable that the combination of the body's sustained immune response and the constant release of antigens of a hypothetical slow virus (schizovirus) may account for the neuro-behavioural alterations. In the following paragraphs, the author discusses how viral pathogens and other potential contributors could interact and lead to schizophrenic psychopathology.

Immune Responses

Neuro-developmental theories of schizophrenia fit the hypothesis that viral insult occurs early in sufferers, not proximally to a psychotic episode. The interaction between host and virus is affected by coordinated activity of the immune system and the brain. There is evidence that schizophrenia is accompanied by mutations in the immune system. Innate immunity is the first defence against microbes; infection results in invasion by live microorganisms and their toxic products, stimulating an inflammatory response. Neuronal functions are disrupted by pathogens and the brain's inflammatory responses. Non-cytolytic viruses may affect neurones without causing cyto-architectural alteration, but disturbing neurotransmitter production and weakening hormones involved in neurodevelopment. [38] In schizophrenia, immune infiltration is absent, as are vital inclusion bodies and minimal gliosis. There is subtle disruption of neuronal function and brain development, but no significant loss of neuronal cells. Thus, the schizophrenia subset may have a viral aetiological origin, bringing about anomalous, specific immune responses, an autoimmune basis, or both. What triggers the autoimmune process is uncertain, but microbial triggers are a strong possibility.

Immune dysfunctions including lymphocytic abnormalities, protein abnormalities, auto-antibodies, and cytokines have been suggested in seriously-ill patients [39]. One study showed significantly higher plasma levels of interleukin-6 (IL-6) in schizophrenics, and soluble IL-6R and soluble IL-2R were significantly high in mania. [40] A few early investigators claimed to have microscopically visualised virus-like particles in the cerebrospinal fluid (CSF) of patients or in chicken embryos inoculated with CSF. Studies of viral antibodies, viral antigens, viral genomes, the cytopathic effect of specimens on cell cultures, and animal transmission experiments are other avenues for exploring the viral infection hypothesis.

The subset of schizophrenics in question may have a highly-sensitive surveillance system, but a less-discerning immune mechanism than the general population. It could be the over-reaction of the immune system to the microbial adversary that may eventually lead to the schizophrenia pathogenesis. The fault may lie in the surveillance system, as well as in the body's anomalous response to the microbial invasion. [17] In general, innate and acquired immune mechanisms interact and cooperate, but any derangement can lead to deviant immune responses that may result in neuropsychiatric abnormalities.

From an evolutionary perspective, innate immunity is less evolved and the mammalian brain is endowed with a complex immune response system, implying that the neurobehavioral aberrations of schizophrenia could be more linked with deviant and vigorous specific immune responses. [17] It is possible that the proposed subset of schizophrenia may have either an autoimmune basis or a viral aetiological origin, bringing about anomalous, specific immune responses, or both. It has been argued that a gene family involved in the specific immune system and autoimmunity is involved in schizophrenia. [41] The genome-wide association studies (GWAS) have been disappointing in schizophrenia, whereas the major histocompatability complex (MHC) region continues to be the best replicated.

Epidemiological Findings

Epidemiological studies offer useful supporting evidence for viral aetiology (see Table 4). Epidemiological studies characterised by certain broad patterns of incidence and distribution of schizophrenia offer evidence to suspend the scepticism of the viral causal hypothesis. In a study of adults at risk of exposure in utero to the 1957 influenza A2 epidemic in Helsinki, those at risk during the second trimester had significantly more hospitalisations for schizophrenia than those potentially exposed during the other trimesters or immediate years. [42] Researchers for nine subsequent epidemiological studies scrutinised the risk of schizophrenia after possible intrauterine exposure to influenza in Europe and the USA; these identified a small majority claiming to find an association.[43] Falsifying the influenza link with the origin of schizophrenia does not

altogether make the viral aetiology null and void. There could still be an unknown virus (schizo-virus) as the causative agent. The Hepatitis C virus came to medical attention only 15 years ago. At least these epidemiological studies illustrated that viruses can help set the stage for schizophrenia as a long-term sequel

Table 4 - Suggested Evidences for Viral aetiology

A. Direct evidences:
1.Neuropathology
2.Transmission to laboratory animal
3.Detection of viral genome
4. Sero-epidemiological studies-Detection of Antigen or antibody
B. Indirect evidences:
1.Seasonality of schizophrenic births
2.Prevalence studies
3. Immune alterations
4.Antiviral effects of antipsychotic drugs
5.Possible immunosuppressant effect of antipsychotic drugs
6.Studies of identical twins
7. Migration and high risk
8. Gender differences-males are younger at disease onset and have a more severe course.

A worldwide average of 1% prevalence of "core schizophrenia" is generally accepted, [44] even though such a concept of universal distribution and gender equality has opposition. [45] However, there is evidence to assume that there may not be gross variations in this global prevalence. Cross-culturally stable rates, despite decreased fecundity in affected individuals, support an external biological aetiology. These point toward biologically-interlinked and multifactorial causation including an evolutionary genetic factor, as a single biological factor would be insufficient. The preservation of susceptibility genes for schizophrenia in the human gene pool is an evolutionary enigma; gene carriers or first-degree relatives may have some compensatory evolutionary advantage. [46] In a multifactorial aetiological model of schizophrenia, infectious theories are contestable. [17]

Such a consistent prevalence, if true, could also be argued in favour of a biologically-inter-linked and multi-factorial causation of schizophrenia, as it is obvious that a single biological factor would be insufficient to maintain a delicate and consistent global prevalence of a disease. Many viruses are relatively constantly distributed, while genetic diseases present distinct geographical clustering due to inbreeding. One may hypothesise that where viral loading is high, genetic input may be less and vice versa. The consistent global incidence points toward universal microbes, a readily-available environmental factor, or, more specifically, a "schizovirus" . The interaction of vulnerable host genes with a virus could yield epidemiology like that of schizophrenia.

Birth patterns rank highly among epidemiological observations in schizophrenia. [47] Many more schizophrenics are born in winter and spring than in summer and fall. [48] Infectious aetiology is a plausible explanation, as many viruses show a surge in the same months and viral aetiology is a more convincing explanation of the consistency in question. While gene coding for particular proteins is inherited, environmental and developmental factors are undoubtedly implicated in modulating genes' expression.

Exposure to prenatal infections and other obstetric complications are neuro-developmental assaults that increase vulnerability to schizophrenia. [49-52] In obstetrics, infection in the mother generates antibodies transmitted to the foetus, producing auto-antibodies that upset neural development and increase the schizophrenia risk. [53]

Schizo-Virus or any Microbe?

It is not certain whether it is body's abnormal response to any virus and other microbes or a specific unknown virus that results in "schizophrenic reactions." It is even unclear that the unbeatable antigens of this hypothetical virus alone are capable of inducing the neuro-behavioural changes associated with schizophrenia. The hepatitis C virus came to medical attention only 15 years ago. The rotavirus was isolated in 1973 and the HIV virus was isolated in 1983. Non-detection of a pathogen does not exclude its role in the pathogenesis. If a specific virus is responsible for schizophrenia, it should have been with human society for a very long time, as the illness has been reported from the beginning of recorded human history. Some people may have a genetic vulnerability to the hypothetical schizovirus; inheritability would lie in contracting the specific virus. Poliomyelitis has a concordant rate of 36% among monozygotic twins; the rest are attributed to environmental factors. The majority of children exposed to the polio virus may not develop poliomyelitis and a genetic propensity may be required for the viral manifestation. It is even reported that 10% of the world population rarely catch influenza, in spite of its yearly mutation.

Cardiac disease due to endocarditis (caused by an autoimmune process affecting many parts of the body), a sequel to acute rheumatic fever, is an analogy to demonstrate how, theoretically, a microbial infection may lead to impaired neurodevelopment and psychiatric disorders in a different scenario. Endocarditis is triggered by a reaction to streptococcal bacteria, not a bacterial infection. It may begin a chronic process, leading to valvular cardiac disease. Generally, rheumatic heart diseases are diagnosed 10 - 20 years following rheumatic fever. Similarly, schizophrenia could be an autoimmune complication of a subtle microbial infection; finding and countering the antigenic triggers of ADs may lead to an effective cure.

HIV/AIDS

Patients with HIV are at risk for developing psychiatric symptoms and disorders similar to those seen in the general

population, as well as those that are direct effects of HIV. HIV is a neurotropic and lymphotropic virus that causes immune suppression and allows the entry of opportunistic pathogens with an affinity for the CNS. There is some evidence that HIV may trigger a psychotic episode and contribute to first-onset schizophrenia. [54] Serious CNS complications occur late in the course of HIV infection, when the immunity function has diminished considerably. The viral load is closely associated with the degree of cognitive impairment. HIV-associated dementia (AIDS dementia complex) is defined as acquired cognitive abnormality in two or more domains and is associated with functional impairment and acquired motor or behavioural abnormality in the absence of other aetiology. It is estimated that 30% to 60% of patients experience some CNS complications during the course of their illness and 90% reveal neuropathological abnormalities at autopsy.

Pearce argued that HIV-related encephalitis could engender a scenario for a viral aetiology of schizophrenia. [17] HIV produces symptoms after being latent for several years. HIV was not identified as the aetiological agent of AIDS until the conditions for viral replication in lymphoid cell lines were identified. Prior to the evolution of PCR serology techniques, it was debatable whether the virus was in circulation at all. This indicates that the absence of a demonstrable virus does not mean the absence of a subtle virus-induced disease process. No virus, as such, is currently detectable in the schizophrenia disease process. Even in the absence of opportunistic infections, HIV infection of the brain causes severe neuro-behavioural syndromes, such as AIDS dementia, without infecting neurons, but by complex interaction with host molecules and non-neuronal cells. All these suggest that a rare or unknown infectious agent is involved; it would not be identified unless it was specifically tested for.

The finding that the neurophysiological and psychological stress of HIV infection can aggravate an underlying psychotic illness implies that viruses, without being a direct causative agent in psychotic episodes, can unmask pre-existing psychiatric vulnerabilities, acting on the brain physiology through unknown pathways. A curious aspect of HIV-related psychosis is that it responds to anti-psychotic treatment and to anti-retroviral drugs. Several anti-psychotic drugs have been shown to have antiviral properties, both in vitro [55] and in vivo. [56] The deduction is that a virus could initiate events resulting in psychosis, and anti-psychotic drugs can interrupt that sequence. All these features of HIV infections are consistent with the idea that a virus can cause neurobehavioral abnormalities after several years.

Borna Disease Virus

It has been recognised that Borna disease virus (BDV) could cause neuropsychiatric complications including neurological, behavioural, and mood alterations in animals. [57] A ribonucleic acid (RNA) virus from the family *Bornaviridae*, it is a neurotropic virus with an affinity to a variety of hosts, particularly hoofed animals, and can cause persistent infection of the CNS. Such an infection may be either latent or chronic and slow, but BDV presents with the latent type, characterised by a lack of viral particles. It may resemble the alleged pathogens in non-affective psychosis. The severity of clinical symptoms depends on the immune response of the host.BDV can directly influence the CNS through the binding of viral proteins with neurotransmitter receptors and indirectly through immune response and inflammatory reactions.

Depending on the host's age and the integrity of the immune response, an infection may be asymptomatic or involve a broad spectrum of behavioural disorders. The severity of clinical symptoms depends on the immune response of the host.[58, 59] Unusual features of BDV biology include nuclear localisation of replication and transcription, varied strategies for the regulation of gene expression, and interaction with signalling pathways, resulting in subtle neuropathology.[60] BDV can directly influence the CNS through the binding of viral proteins with neurotransmitter receptors and indirectly through immune response and inflammatory reactions. The issue of human BVD infection has been recently questioned by American researchers who reported an absence of association of psychiatric illness with antibodies to BDV or with nucleic acids in serially-collected serum and white blood cell samples from 396 participants. [61] However, BDV in animals helps to bring the infection-based model of schizophrenia to the realm of the scientific imagination.

Neurotransmitters

It is an overstatement to say that schizophrenia is a neurotransmitter disease, although it is well established that it incorporates a derangement of dopamine activity. Some viruses have been shown to alter dopamine metabolism. [62] The literature deciphering the role of viruses in bringing about neurotransmitter abnormalities linking neurodevelopment assaults and the neuropsychological manifestations of schizophrenia is unhelpful. [63] It has been reported that in rodents, BDV could crash neurotransmitter systems, including dopamine, neuropeptides, and glutamate. [64] How viruses alter neurotransmitters is a central issue. Communication between the immune system and the brain is crucial to defend against viral infection; this is mediated through neurotransmitters. Viruses are bound to tamper with the intrinsic communication system as part of their cellular offensive. Some viruses have been shown to alter dopamine metabolism. [65]

Genetics

The undisputed genetic factor in schizophrenia may be posited to discount the viral hypothesis. However, genetic factors do not exclude environmental contributions. Monozygotic twins have a concordance rate of only 48%. Brief reactive psychosis due to acute sequels to viral infection, though regarded as unrelated to schizophrenia, may still be schizophrenic reactions and they do not progress to schizophrenia only because the sufferers are not genetically predisposed to schizophrenia.

Genetic predilection may be attributable to genes that determine idiosyncratic differences in immune responsiveness to common viral pathogens.

Susceptibility and immune response to infectious agents are known to be subject of genetic control and may involve multiple interacting susceptibility genes.[66] The genetic component of schizophrenia may engross multiple interacting susceptibility genes. These together or singularly may moderate the virus, and the virus and gene product may act at different points. Many cases would have a genetic foundation and it may be extremely rare to develop schizophrenia independently of a genetic anomaly. A small subset of patients may have a purely genetic form. Research should also be directed at identifying risk genes and why they assert themselves and cause the disease. Any future research which sheds more light on some people are affected more readily than others would bring researchers closer to more effective treatments and early intervention (see Table 5).

Table 5 - Future Directions

1. Critical research studies should target in establishing the viral and autoimmune aetiology of a subset of schizophrenia as the illness may be due to both factors. Detection criteria/ tests are vital in isolating this subset from the rest of schizophrenia syndromes 2. Robust epidemiological studies to be conducted to find putative infectious agents and possible models of transmission.
3. Developing new methods for detection of viral agents, directed at the analysis of previously identified pathogens and identification of novel viruses. Vigorous studies with PCR and other sensitive methods for nucleic acid detection to be carried out for the detection of viral nucleic acids in the body fluids of schizophrenia sufferers.
4.To find a method to turn off autoimmune attacks from the body or selectively disable the immune response
5. Identify risk genes and to find the specific DNA molecules and their tagging patterns vital for the progress of the illness.
6. To develop drugs to target specific genes which would mean they would be far more effective and have fewer side effects.
7. Finding psycho-physiological parameters for early detection to minimise the damage.
8. In the event of future discovery of effective antiviral agents, the subset of schizophrenia in question could take advantage of the clinical benefits of such discoveries.
9. Viral aetiology, if proven true, could lead to finding a vaccine against the disease.
10. Selective immune-suppressants could be a future addition into the psychiatric armamentarium.
11. A derivative of cloazapine without its haematological and metabolic side effects would be highly promising.

Summary

There are multiple interlinked causative factors in schizophrenia and viral infection may be only a trigger. Viral infections may be the cause of vigorous immune responses or triggering an autoimmune process that lead to neuro-behavioural aberrations and a subset of schizophrenia would emerge as viro-immuno-neuropsychiatric disorder or autoimmuno-neuro-psychiatric disorder. If such a subset of schizophrenia contains an autoimmune component, either triggered by infectious agents or due to unidentified intrinsic factors, the disease process would be determined by genetic vulnerability. There is not sufficient evidence established to identify viruses as being implicated in the aetiology of schizophrenia, but researchers have reason to anticipate further laboratory studies, as newer, more sensitive laboratory technologies are evolving. A viral or autoimmune model of schizophrenia may illuminate its pathogenesis, but not necessarily the diversity of psychiatric symptomatology. In the last few decades, schizophrenia research has been focussed on neurotransmitter derangements and neuro-developmental anomalies. The cause of a tsunami is not in the sea water, but due to the tectonic shifts under the sea bed; the aetiology of schizophrenia may be similarly due to immune alterations.

Pellagra psychosis due to niacin deficiency was hidden under the schizophrenia umbrella.[67] There may be other psychotic disorders grouped under schizophrenia, and they may have a pure biological aetiology—chemical or infectious—but with genetic vulnerability. No one can be sure whether it is the toxic chemical of the pathogens or the immune response of the host, or both, that may lead to the psychopathology. Searching for this hypothetical virus is a challenging task, but if researchers found it, the benefits would be enormous. A viral aetiology of certain types of schizophrenia, if demonstrable, could affect radical changes in treatment and management. In fact, the hypothesis of viral aetiology is more promising than any other biological hypothesis, as it gives a message of potential drug cure. In this contest, it is interesting to note that the antigenic similarity between components of the streptococcus and cardiac tissue resulted in rheumatic heart diseases, but with the advent of penicillin, this disease has virtually disappeared. Only time will determine the validity and therapeutic prospects of the viral and autoimmune aetiology of schizophrenia.

Davison opined that as evidence accumulates about the autoimmune basis of at least a subset of psychiatric disorders, clinicians should keep abreast of immune-neuropsychiatric research.[68] Psychiatry must constantly expand to meet the growing needs with the emergence of novel ideas in other medical specialities and it is high time to introduce a new terminology—"Psycho-immunovirology"—to study the viral aetiological mechanisms involved in psychiatric disorders like schizophrenia. Neuro-virology and psycho-immuno-virology could develop as an interdisciplinary field which represents a melding of virology, psychiatry, the neurosciences and immunology.

Competing Interests
None declared

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