Virus Infection as a Cause of Inflammation in Psychiatric Disorders

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Abstract

Many neurotropic viruses exist and may cause classical inflammation but also low-level neuroinflammation. However, viruses may be dormant within the CNS and become active later. The role of neurotropic virus infections in the causation of psychiatric disorders may be underestimated, because the diagnostic approach to the CNS is difficult and to dormant infections in general, but especially within the CNS. Evidence is increasing that infections increase the risk of psychiatric disorders, not only prenatal infections but also infections during the lifetime. The question how low level neuroinflammation may be involved in severe psychiatric disorders like affective and schizophrenic spectrum disorders is intriguing but remains to be studied. Experimental data clearly show that low-level neuroinflammation can be induced by viruses, but the definitions of inflammation and low level neuroinflammation appear to be blurred and apparently the previous classical definition of inflammation has to be widened. Virus infection itself or virus-related products or virus-induced autoimmunity may play a role in disease pathogenesis. More sensitive diagnostic approaches from neuroimaging and CSF investigations may hold the key to a better understanding and definition of CNS viral infections as an etiopathogenetic subgroup of severe psychiatric disorders.

Viruses are ubiquitous infectious agents which for the major part contain only genetic information for replication in the host cell. Virus infections may induce classical inflammation, but many viruses may induce little or no inflammation and seem to be of overall low pathogenicity for the infected host. The latter aspect is an evolutionary advantage, because adaptation to the host may increase the overall likelihood of being able to replicate for a long period, whereas highly aggressive agents tend to eradicate not only the host but in parallel reduce their own chances of replication. These evolutionary aspects are a precondition for complex interactions between the infecting agent and the host and therefore a priori many virus infections and their consequences tend to be complicated, and may often become dormant though may reactivate at some time point or lead to slight dysfunction over time [1]. The etiopathogenesis of psychiatric disorders to a considerable extent remains unclear or even unknown, although a large subgroup of psychiatric disorders, especially the so-called endogenous or idiopathic psychoses (like schizophrenia, bipolar disorder, severe depression), seems to be based on biological grounds, and a biological core in the pathophysiology and
Pathogenesis seems to prevail. A possible role of low-level neuroinflammation (LLNI) in the pathogenesis of these disorders, induced by viruses and other infectious agents, was outlined in the mild encephalitis hypothesis, which was proposed to differentiate from classical encephalitis in that only very short-lived small classical lesions in the CNS may arise or even no classical inflammation may be observed; instead, there was exclusively LLNI, which remained to be more clearly defined [2]. This hypothesis was exemplified in Borna disease virus (BDV) infection, for which there is still lack of proof in humans. BDV represents a frequent cause of meningoencephalitis in horses and sheep in Middle Europe and can infect nearly all species (overview about various aspects in [3]). Evidence has accumulated that BDV infection is also a rare cause of neurological and psychiatric disorders [4–7], although a hype of publications claiming to have identified BDV sequences had to be corrected as having been due to laboratory contamination [8]. This recent experience with the difficulties being confronted when trying to identify virus association in etiopathogenetically unclear psychiatric or neurological disorders, illustrates the methodological difficulties involved, making understandable, at least in part, the difficulties of finding the paths into research on the viral causes of psychiatric disorders, and to identify LLNI. The idea that viruses may underlie etiologically unknown psychiatric disorders is not new. At the beginning of the 20th century and over decades, a virus hypothesis (bacteria and viruses were only beginning to be differentiated) was a mainstream idea, but proof remained open and thus the ideas disappeared more and more. Only recently can a reappraisal of such a hypothesis be observed, because more and more studies are demonstrating a risk increase from infections for psychiatric disorders. A most striking result, which can be considered proof of the concept, was a large epidemiological study carried out over 30 years in Denmark, demonstrating an additive risk increase for various psychoses due to severe infections and autoimmune disorders [9]. It is of notice here that leading immunologists now think that infections generally may contribute to autoimmune disorders, though proof for this is still lacking (cf. the long debate about virus infections in multiple sclerosis, now supported by recent histopathological findings [10]).

Here the current situation of epidemiological and pathophysiological findings in the psychiatric research field will be outlined beginning with a look back into the long history of the subject.

A Look Back into the History

The idea that viruses may cause psychiatric disorders has been voiced for nearly a century, but the proof of a causal role for viruses was difficult or only successful in rare single cases [11]. Nevertheless, a large number of virus infections are known to rarely cause psychiatric disease. The most frequently identified infection is herpes simplex virus encephalitis which can induce a range of psychiatric syndromes, usually accompanied by severe organic psychoses due to severe infections and autoimmune disorders [12]. Today, it is often reported that the elucidation (and the diagnosis) of organic causes of psychiatric disorders does not appear to be very complicated or challenging. However, this is a misinterpretation [13].

When looking into the details of the history of psychiatric disorders which are now clearly associated with infections, it appears that also in history the path to an etiological diagnosis was rather difficult. For example, the elucidation of the etiology of general paresis was characterized by long controversial discussions in the scientific field, and the majority of researchers, not least the histopathologists, rejected even the hypothesis that syphilis may be an important risk factor [cf. 14]. One of the earliest ideas that syphilis may represent a risk factor for general paresis was...
proposed by Esmarch and Jessen [15], initiated by single case observations. The first statistical data (a term not yet used at the time) were provided by Erich Mendel in the 1880s. His conclusion that syphilis may be an underestimated risk factor in addition to other risk factors, which were considered psychological and genetic, was heavily criticized so he took a step back. Only after seven decades from the first hypothesis to the detection of spirochetes by Noguchi and Moore in 1911, and after the introduction of lumbar puncture by Quincke and the Wassermann reaction (representing an antibody test), the reluctance against a causality hypothesis between syphilis and general paresis or tabes dorsalis was declining. Another important insight was that a similar histopathological picture, inflammatory vs. degenerative type of general paresis, was nearly identically seen with experimental toxoplasma infection. Thus, the idea emerged that a general type of pathogenesis was associated with CNS infections was used to explain the histopathological picture but not the specific infection itself. In fact, in the present knowledge about syphilis, a number of questions remain open with regard to the degenerative and inflammatory aspects of infectious diseases. In retrospect, the clinical categorization of general paresis by Mendel with regard to psychopathology was perfect but rather arbitrary and negligible concerning the understanding of its underlying pathogenesis. The important aspect not solved up to now is the overall low pathogenicity of syphilis infection, in that only some of the infected subjects may develop CNS disease and that often only after long latent period. The limited knowledge about these aspects was surely one reason to undertake unethical studies like the Tuskegee study and a similar study in Guatemala (by US researchers), for which President Obama recently apologized: to observe untreated syphilis over the long-term and to possibly learn why and how the persistent infection may at some time point or another become pathogenic for the infected host. Though unethical, these studies demonstrate the unsolved scientific questions involved in persistent infections or pseudoscientific thinking. A rather similar problem prevails with late Lyme disease, and the ethical problems to neglect or overestimate were repeatedly debated hotly [cf. 16]. Apparently, we do not have the choice to make research easy, but have to deal with complicated questions involving complex research approaches.

These prevailing problems to understand the pathogenesis of CNS infections are further highlighted in three well-studied infections including viral infection (rabies, cerebral malaria, and African trypanosomiasis), which demonstrates in detail, as brains and a lot of studies are available, that the pathogenesis of these CNS infections over time is extremely complex and variable, that similarities but also differences exist, and that insights into one disease can only in part be applied to another type of CNS infection as each agent has different consequences because of the details of its pathogenesis [17].

Such complicated backgrounds and differences in pathogenesis have to be kept in mind when dealing with the question of CNS inflammation caused by viruses possibly underlying psychiatric disorders. A view that one size fits all can be assumed to be very unlikely. Furthermore, in virus infections the interaction with the host is generally rather close, as viruses mainly represent genetic information, and it is no surprise that many neurotropic viruses exist, most of which with overall low pathogenicity, posing a major difficulty for research because only in a minority of the infected subjects does a certain disease develop [18]. Nevertheless, new viruses are being detected every year and may be of possible relevance for human disease. Furthermore, one should be aware that a number of infectious agents may not have been identified yet. A recent large study in California, suggested that even during the acute phase of meningoencephalitis there is only a less than 50% chance of identifying the respective etiology of the disease [19].
Borna Disease Virus Infection

Over many years, our work has been dealing with the possible role of Borna disease virus (BDV) in neurological and psychiatric disorders of humans [7]. BDV is the strongest known neurotropic virus. The research proved to be rather complicated and the interpretation difficult as the likely low overall pathogenicity together with the general unspecificity of symptoms in all known organic causes of a psychiatric disorder generally poses still unsolved problems for research. From this perspective and experience the issue of virus infection as a cause of inflammation is reconsidered and reviewed here.

From our research on the possible role of BDV infection for human neurological and psychiatric disorders we accumulated evidence in thousands of patients tested with the indirect immunofluorescence assay for BDV antibodies and found a prevalence of about 5% in our psychiatric sample, whereas only about 3% was found in surgical controls [2, 7]. The specificity of the human BDV antibodies was confirmed, recognizing linear epitopes of BDV proteins [20]. Attempts were made to isolate virus from CSF and postmortem brains which to date remained unsuccessful [cf. 4 and unpubl.]. Nevertheless, we found cases, though very few, in which BDV antibodies were produced within the intrathecal spaces (increased antibody index = AI), demonstrating that the specific agent was BDV and was likely to have induced CNS infection [21, 22]. This method to quantitatively validate antibodies by comparing blood to CSF levels is now well established and considered valid to indicate any specific type of encephalitis [23, 24]. Nevertheless, proof of human BD is yet to come. Overall, we suggest that a maximum of 3% of psychiatric cases might be causally related to BDV infection but very few cases fulfilled the probable criteria of BDV-associated mild encephalitis only [cf. 21, and unpubl.].

An interesting aspect is that it has now been shown that BDV sequences are integrated into the human genome [25, 26] and these findings raise new questions on the possible pathomechanisms involved [27]. A similar scenario is with another endogenous retrovirus, HERV-W, which has been found in both, in multiple sclerosis and in schizophrenia, the mechanisms involved seemed to relate to inflammation [28–30]. One should keep in mind that viruses in general may be able to cause CNS dysfunction, for example neuronal dysfunction without any sign of inflammation, which was termed the molecular anatomy of virus disease [31]. The question how to differentiate LLNI from noninflammatory dysfunction due to virus infection is, however, open.

Definitions of Inflammation and Neuroinflammation

The definition of inflammation has widened during the last years from results of extensive experimental inflammation research. Now, inflammation is understood as ‘a complex set of interactions among soluble factors and cells that can arise in any tissue in response to traumatic, infectious, posts ischemic, toxic or autoimmune injury’ [32]. This broad understanding of inflammation is apparently justified, but has only been established preliminarily in the clinic not forgetting the always limited possibilities in the clinical diagnostic approach for practical and ethical reasons as compared to the experimental approach. Nevertheless, a considerable number of new markers of inflammation were also established in the clinic in the last years, e.g. approaches like proteomics are rather promising to improve diagnostic sensitivity. But several types and aspects of nonclassical inflammation were only recently recognized and only partly classified, e.g. a long-known type relevant for example in leprosy was renamed ‘parainflammation’,