NEWS

Infections and neuropsychiatric disorders: new studies document pathways to prevention and treatment

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While long suspected, the fact that some cases of human brain disorders are related to infections entered the realm of modern science with the discovery in 1905 by Schaudinn and Hoffman that neurosyphilis is caused by the organism *Treponema pallidum* [1]. The relationship between infections and neuropsychiatric disorders was further bolstered by the identification of a range of psychiatric disorders following pandemics, particularly the "Spanish Flu" pandemic of 1918–19 [2]. Since that time there has been an increasing understanding of the complex interaction of infectious agents and the immune system within the CNS based on studies of postmortem human brain as well as animal and cellular models. Epidemiological methods also have contributed to an increased understanding of the role of infections in human neuropsychiatric disorders by linking exposures to subsequent outcomes as well as to serological evidence of past infection [3].

The importance of infections in human neuropsychiatric disorders has been brought to the forefront by the recent Covid-19 pandemic where there are documented associations between infections with the SARS-2 Coronavirus and increased prevalence of a range of neuropsychiatric and neurodegenerative disorders [4]. Three recent publications address different aspects of the association between infections and neuropsychiatric disorders and highlight potential pathways for interventions.

Wainberg et al. [5] provide a comprehensive review of evidence linking herpesviruses to Alzheimer's disease (AD). After noting that the potential association goes back many years and has been controversial, they review a number of recent publications which are supportive of this association. These include studies in animal models, postmortem human brains, and human cellular models as well as epidemiological studies in human populations. A majority of the studies of postmortem brain and human populations have documented increased rates of herpesvirus infections in individuals with Alzheimer's disease although the strengths of association and the specific herpesviruses which are implicated have varied among studies. Nonetheless, these studies document that human herpesviruses can persist in the human CNS in the absence of the frank encephalitis which has been thought to be characteristic of untreated infections. Weinberg et al also discuss parallel studies in mouse models indicating that amyloid beta and neuroinflammation can serve as part of a protective response to viral infection but can become pathogenic over the long term due to the toxic effects of these molecules.

The link between herpesviruses and Alzheimer's disease is also supported by recent epidemiologic studies documenting an association between prior exposure to infectious agents and the subsequent development of Alzheimer's disease or cognitive impairment. The association of herpesvirus infection and these outcomes is further supported by genetic studies suggesting gene by environmental interactions involving *APOE4* as well as other genes associated with increased risk of Alzheimer's disease.

Despite these associations, the authors point out several limitations of these studies. Potential limitations include the possibility of reverse causation, that is, that the herpesvirus infection may have occurred after the onset of the Alzheimer's disease process, perhaps as a result of altered behavior or reduced cognitive functioning. They also note that genetic associations may be affected by undetected population stratification. They thus highlight the importance of ongoing treatment studies of antiviral medications for Alzheimer's disease and age-related cognitive impairment. They point out the need for early intervention given the potentially long lag time between the onset of the Alzheimer's disease process and the clinically detectable signs and symptoms.

The association between infections and psychiatric disorders is further explored by Levine et al. [6]. These investigators examined data from two large national databases to study the association between a range of infectious disease exposures and the subsequent development of six neurodegenerative disorders: Alzheimer's disease, amyotrophic lateral sclerosis (ALS), Parkinson's disease, generalized dementia, vascular dementia, and multiple sclerosis. They first interrogated the FinGen dataset which consists of samples collected by a nationwide network of Finnish biobanks, a set that currently has data on more than 342,000 individuals relating to 2202 disease endpoints. Associations that were found to be statistically significant in this dataset corrected for multiple testing were tested for confirmation in the UK biobank. This widely used dataset consists of genetic and phenotypic information on more than 500,000 individuals living in the UK.

Employing this strategy, the investigators identified 45 infectious disease exposures significantly associated with increased risk of neurodegenerative disease in the FinnGen population and replicated 22 of these associations in the UK dataset. In cross-sectional analysis, generalized dementia had the most replicated associations with six viral groupings showing significant results: viral encephalitis, viral warts, all influenza, influenza and pneumonia, viral pneumonia, and other viral diseases not elsewhere classified. There were 5 associations with Parkinson's disease, 4

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with Alzheimer's disease, 4 with vascular dementia, 2 with multiple sclerosis, and one with ALS.

Influenza infections with pneumonia were the exposures that had the most associations with neurodegenerative disorders being associated with five of the six disorders which were examined. Other infections associated with neurodegenerative disorders included CNS infections such as meningitis and viral encephalitis as well as infections ascribed to human herpesviruses and human papillomaviruses. There were also associations with presumed viral infections of the liver and intestinal tract.

The longitudinal nature of the FinnGen population allowed the authors to examine the timing of the exposure and the development of the neurodevelopmental disorder for 16 of the 22 replicated associations. Of these, 6 remained significant from 5 to 15 years before the diagnosis of the neurodegenerative disorder. These included the relationship between influenza pneumonia with Alzheimer's disease and with dementia. Viral warts were also associated with subsequent dementia, confirming a somewhat surprising finding previously reported in another population [7].

Relevant to Levine et al., infections with Herpes Simplex virus were significantly associated with Alzheimer's disease and generalized dementia in the period 1–5 years before disease diagnosis but not within the year prior to diagnosis. This finding makes reverse causation unlikely and highlights the importance of longitudinal studies in establishing causative relationships between infections and human brain disorders.

The timing between exposure and diagnosis was further determined by examining the hazard of becoming infected after the diagnosis of a neurodegenerative disorder as compared to a similar time period before diagnosis. In almost all of the cases where such data were available, the hazard ratio for developing a neurodegenerative disorder after a viral exposure was substantially higher than the hazard ratio for the reverse order of events.

As in the case of Levine et al., the authors point to the value of clinical trials of antiviral agents. They also point out that many of the infections linked to neurodegenerative disorders in their study are partially preventable with vaccines that are licensed in the United States and other countries but are not universally used. These include vaccines for varicella-zoster, human papilloma, and influenza viruses as well as "pneumonia" vaccines directed at *Streptococcus pneumoniae*.

The authors also point out that exposure to many of the viral agents can be identified in blood samples from patients using widely available immunoassays and they suggest adding these to the tests obtained as part of age-appropriate routine clinical care.

An additional approach to link exposure to infectious agents and neuropsychiatric outcomes involves the measurement of these outcomes before, during, and after exposure to microorganisms during the course of an epidemic. Yuan et al. [8] employed this approach to examine the relationship between mood disorders and the ongoing Covid-19 pandemic caused by the SARS-2 Coronavirus as well as other recent epidemics. They searched 15,869 publications available before Aug 14, 2020, and used established meta-analytical techniques to identify 283 studies that met predefined criteria. These studies contained relevant data on more than 940,000 individuals consisting of a number of populations of interest including healthcare workers, older adults, pregnant women, university students, infected patients, and survivors of infection as well as the general public. The studies included 255 studies directed at the ongoing Covid-19-SARS-2 pandemic, 18 studies focused on the 2003 outbreak of severe acute respiratory syndrome (SARS) caused by the SARS-associated coronavirus (SARS-CoV) as well as four studies directed at the Middle East respiratory syndrome coronavirus (MERS-CoV), three studies directed at the H1N1 strain of influenza virus, two studies directed at Ebola virus and one study directed at Zika virus. The studies included populations from 45 different countries.

The study documented unusually high prevalence rates of mood disorders during the epidemic periods. The mean prevalence rate of what was characterized as moderate depression in the general population was approximately 20% and the prevalence of moderate anxiety was 30%. The rates of these disorders did not differ significantly between the ongoing Covid-19-SARS-2 pandemic and the 2003 outbreak caused by SARS-CoV. There was not sufficient data to determine corresponding prevalence rates for the other epidemics which were examined.

In terms of individual risk factors, as expected, the highest rates were noted in individuals with a diagnosed mental disorder, individuals with confirmed or suspected infection, or those with infected colleagues or family members. Increased prevalence of these disorders was also associated with individual factors including being female, older than 40 years of age, or unmarried. An increased risk was also associated with having a lower level of education as well as cigarette smoking or alcohol consumption. On the other hand, lower levels of mood symptoms were associated with good social support and frequent exercise.

The authors were also able to investigate changes in the prevalence of mood symptoms during their period of study of the Covid-19 pandemic. The prevalence of depression, anxiety, and insomnia increased among the general public, health workers, and university students. It is of note that the study period ended in August 2020 and thus did not include the more recent surges of infection relating to Omicron and other variants. The authors conclude with a "call for action" in terms of population-based approaches to the lowering of the rate of mood disorders by the prevention and management of infectious disease outbreaks.

The above studies provide clear evidence for an association between infectious events and a range of neurological and psychiatric disorders. These studies also demonstrate the value of population-based analyses supported by nationwide databases and related resources. However, since these studies are predominantly population-based, some questions remain to be answered in terms of individual risk factors, particularly regarding the effects of epidemics. For example, it largely remains to be determined how much of the risk for psychiatric disorders which occurs during epidemics is related to individual exposures as opposed to problems associated with living during the pandemic such as social isolation, food shortages, and other stressful situations. This is particularly the case for individuals whose lives are already affected by a psychiatric or physical disorder [9]. These questions can be addressed by the study of individuals in whom both exposure information and psychiatric data are available. Since many Covid-19 infections are not diagnosed during the course of active infection [3], past exposure can best be documented by the measurement of long-lasting specific antibodies in blood samples. Studies employing this approach will be necessary to determine if mild or clinically inapparent infections can lead to neuropsychiatric consequences. Studies based on individual members of a cohort can also document the possible contribution of other environmental exposures such as air and water pollution as well as lifestyle factors such as diet and cigarette smoking which can alter the immune response to viral infections [10].

Finally, it is clear from these and other studies that the contribution of infections to neuropsychiatric disorders is not restricted to a single agent but rather involves multiple agents interacting with both genetic and other environmental factors. Classical methods of association of infectious diseases such as those based on Koch's postulates need to be updated to encompass the understanding of complex disorders, just as the classical concept of Mendelian inheritance has been modified to encompass complex genetic associations and gene-environmental interactions [11]. More comprehensive criteria such as those proposed by Bradford Hill provide a more appropriate framework by incorporating underlying biological, epidemiological, and clinical studies into plausible models of complex disorders [12].

Implicit in these models is the long-term effect of effective interventions on disease prevalence. It is thus imperative that preventative and therapeutic interventions directed at relevant infectious disorders be developed and implemented. In light of the long period between infectious exposure and the onset of many psychiatric disorders, vaccines which can be given in early life and provide long-term protection are particularly important. As noted by Levine et al., this would include the increased utilization of available vaccines for the prevention of viral and bacterial infection. It is also important to accelerate the development of new vaccines which are currently under development including ones for additional herpesviruses [13] and neuropathic enteroviruses [14] as well as to monitor the effect of these interventions on both an individual and population level. This strategy might lead to conclusively defining a causative role for infections in nonregenerative and neuropsychiatric disorders and lead to a decrease in the rate of these life-altering and potentially devastating disorders.

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COMPETING INTERESTS

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ADDITIONAL INFORMATION

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