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Review

Avian influenza and the brain—Comments on the occasion of resurrection of the Spanish flu virus

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Abstract

Recent incidences of direct passage of highly pathogenic avian influenza A virus strains of the H5N1 and H7N7 subtypes from birds to man have become a major public concern. Although presence of virus in the human brain has not yet been reported in deceased patients, these avian influenza subtypes have the propensity to invade the brain along cranial nerves to target brainstem and diencephalic nuclei following intranasal instillation in mice and ferrets. The associations between influenza and psychiatric disturbances in past epidemics are here commented upon, and the potentials of influenza to cause nervous system dysfunction in experimental infections with a mouse-neuroadapted WSN/33 strain of the virus are reviewed. This virus strain is closely related to the Spanish flu virus, which is characterized as a uniquely high-virulence strain of the H1N1 subtype. The Spanish flu virus has recently been reconstructed in the laboratory and it passed once, most likely, directly from birds to humans to cause the severe 1918–1919 pandemic.

Keywords: Infections; Nervous system; Substantia nigra; Parkinsonism; Behavior; Schizophrenia

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1. Introduction

A terror of the past, the virus of the Spanish flu of 1918–1919, has now been reconstructed in the laboratory [45]. Most likely,

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an influenza A virus strain passed directly from a bird to a human being, after which it adapted to the new host to cause the pandemic [41]. Avian influenza is very common, but crossing the species barrier to humans is an extremely rare event. In fact, until recently the barrier between birds and humans was thought to be too great to allow a direct transmission of the virus [52], although all mammalian influenza viruses may originate from ancestral precursors in wild water-fowls [13]. In light of the current incidents in South-East Asia and the Netherlands, in which humans have been infected with avian influenza virus strains [47], the nature of the species barrier and the risks for its by-pass have come into focus. Furthermore, since certain avian influenza virus strains can invade the brain of experimental animals [31], the question whether influenza poses a threat to our brains can be raised [46].

During pandemics in the past, including the Spanish flu, debates were spurred whether influenza is associated with psychosis or neuropsychiatric disorders, and there is a current controversy among epidemiologists whether influenza during pregnancy is a risk factor for schizophrenia in the offspring, or not. In this commentary the early literature on these possible associations will be briefly reviewed, as will factors that may facilitate a spread of the virus from its primary site of infection, the respiratory tract, to the brain and its potential to cause changes in brain gene expression, synaptic activities and behavior.

2. Human influenza pandemics and nervous system dysfunctions

2.1. Post-influenza psychosis in past pandemics

Except for observations of "febrile or initial delirium", mental disturbances in connection with influenza were not described before the 19th century according to Althaus [1]. Then in 1846, case-books report from the Dundee asylum on a "*decided increase in the suicidal melancholic cases*", the servants being more severely attacked than the patients, after influenza first visited Scotland [32]. This early observation was referred to in the intense debate on patients with psychiatric disturbances that included depression, manic conditions, amentias, acute delirious states, hysterical reactions, ideas of persecution and hallucinations during the 1889–1990 influenza pandemic [32]. Skepticisms on these reports were expressed and "*the ready acceptance of influenza as the cause of so many supposed cases of insanity*" was protested [42]. Melancholia seems, however, to have been especially prevalent and an asylum report from this period says that "*the epidemic of influenza* 1889–1990 *left the European world's nerves and spirits in a far worse state then it found them*" [9].

Few pandemics in modern times have within such a short period, 1918–1919, killed so many individuals as the Spanish flu. The mortality rate was about 2–3% and the estimated number of deaths varies between 20 and 40 millions or more. This was several times more than the death toll of soldiers during the First World War; the appearance of influenza in the troops weakened so much the fighting abilities of the armies that it contributed substantially to the end of the war [27]. During the Spanish flu pandemic, post-influenza psychosis was reported both in Europe and in USA. In a study of about two hundred cases of psychoses at the Boston Psychopathic Hospital, one-third showed symptoms similar to schizophrenia, but the majority of these patients recovered completely [23]. The few patients who showed no evidence of recovery may have represented latent schizophrenia precipitated by the influenza, and Bleuler in1924 (cited in [23]) stated that "*neither the grippe nor the war have added to the existence of schizophrenia*".

A major problem with these early attempts to associate influenza with psychiatric disorders is the lack of reliable statistics and standardized clinical diagnostic criteria. In addition, influenza A virus was not identified until it was isolated in ferrets in 1933 by Wilson and Smith [27]. During later years, anecdotal reports of acute psychotic symptoms, i.e. anxiety, confusion, extreme restlessness, ideas of perpetuation and senses of strange, unpleasant smells, have appeared following the Asian influenza in 1957. The symptoms usually receded within 6–8 days, leaving the patients with amnesia of the psychotic episodes (review, see [34,51]). Although reversible post-influenza psychosis may be recognized, its pathogenesis as well as its potential relation to other psychiatric disorders is not clear. However, these debates from past epidemics may stimulate interest in research on effects of influenza virus infections on the brain as expressed in a voice of 1892 stating "*we could not have a more interesting subject*" [48].

2.2. von Economo encephalitis: post-encephalitic Parkinsonism and behavior disturbances—was there any relation to influenza?

In 1916–1927, the world was hit by another pandemic and the disease of this pandemic affected the brain, i.e. *encephalitis lethargica* or von Economo encephalitis. The most prominent inflammatory lesions occurred in the midbrain tegmentum and substantia nigra. Inflammation localized anteriorly in the lateral wall of the third ventricle was observed in patients with insomnia, while in the posterior wall in patients with sopor [50]; a topography that predicted recent hypothesis on diencephalic regulation of sleep [33]. Post-encephalitic Parkinsonism was common and in these patients nerve cell loss and neurofibrillary tangles were seen in the substantia nigra and substantia innominata, the raphe, locus coeruleus, mesencephalic periaqueductal grey matter and hypothalamus [44].

Long-lasting behavior disturbances could appear, particularly in children, either directly after a hyperkinetic phase of the encephalitis or after a time period of recovery. These changes were characterized by manic phases with increased locomotion, and sleep disturbances with attacks of anxiety at night and sleepiness during daytime. Previously normal children became very talkative, obtrusive, disrespectful and unrestrained; they disgraced other people, became asocial, and had outbreaks of anger. They were witty, accosted people on the streets, pinched their clothes, shouted words of abuse and scrawled on walls [49].