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Parkinsonism and Neurological Manifestations of Influenza Throughout the 20th and 21st Centuries

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Abstract

Purpose—Given the recent paper by Jang et al. on “A Highly Pathogenic H5N1 Influenza Virus” which reported a novel animal model of parkinsonism, we aimed to perform a complete historical review of the 20th and 21st century literature on parkinsonism and neurological manifestations of influenza.

Scope—There were at least twelve major flu pandemics reported in the literature in the 20th and 21st century. Neurological manifestations most prevalent during the pandemics included delirium, encephalitis, ocular abnormalities, amyotrophy, myelopathy, radiculopathy, ataxia and seizures. Very little parkinsonism was reported with the exception of the 1917 cases originally described by von Economo.

Conclusions—To date there have been surprisingly few cases of neurological issues inclusive of parkinsonism associated with influenza pandemics. Given the recent animal model of H5N1 influenza associated parkinsonism, the medical establishment should be prepared to evaluate for the re-emergence of parkinsonism during future outbreaks.

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Keywords

neurological; complications; adverse events; flu; influenza; parkinson's disease

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Introduction

Neurological complications as sequelae of influenza infection, although rare, have been documented for over a century. Our understanding of influenza has grown immensely over the last century, yet our understanding of its neurological complications has been largely limited to case reports and case series. As early as the influenza pandemic of 1918, physicians and scientists have examined both the cerebrospinal fluid and post-mortem nervous tissue of flu patients and made preliminary attempts at correlating neurological symptoms [1 - 2]. The general medical symptoms of influenza have been well recognized, and well documented. The neurological manifestations, however, have been more variable from outbreak to outbreak, and we reviewed what has been documented for the past two centuries. Additionally, given the recent publication by Jang et al. that highly pathogenic H5N1 influenza can induce a Parkinsonian pathology in mice, we thought it interesting to review neurological reports of all influenza outbreaks in the 20th and 21st centuries.

Methods

A complete review of the literature (published in English) focusing on influenza outbreaks, and their associated neurological manifestations was undertaken. Neurological complications of influenza were searched utilizing PubMed and Google Scholar and yielded several case reports (n=5), original research papers (n=12), discussions (n=10), reviews (n=14), and one book on influenza and its complications (1889 to the present). The Centers for Disease Control and Prevention's Morbidity and Mortality Weekly Report on H1N1 2009 was also searched for documentation of neurological manifestations of 2009's swine flu outbreak. The review was prompted by the recent observation of an animal model of parkinsonism published by Jang et al. [3].

Results and discussion

Reports of influenza outbreaks dated as far back as 1510, with the first reports of an intercontinental influenza pandemic appearing in 1580. The earliest pandemic for which there were detailed records occurred in 1889 [see table 1]. The pandemic of 1889 touched every continent and killed approximately one million people [4]. While the burden of the morbidity and mortality related to influenza is due to its effects on the respiratory system, evidence of influenza's neurological manifestations appeared in the earliest accounts of influenza outbreaks. Dating back to 1580, the accounts included descriptions of postinfluenza encephalitis [4]. When reviewing historical accounts, it is important to recognize that many reported cases of 'the flu' may not have been due to the actual influenza virus.

The most famous influenza pandemic, the one to which all other pandemics have been compared, was the pandemic of 1918, also known as the Spanish flu [1, 4-5]. An estimated

500 million people worldwide were infected between 1918 - 1919, and thus there were many opportunities to observe its neurological manifestations [6].

The British Royal Society of Medicine published their *Discussion on Influenza* in 1919 [1-2, 5, 7]. This work included discussions on the neurological illness and its apparent relationship to the pandemic. E.B. Turner related his experience with the influenza epidemics of the late 19th century [5]. He postulated that influenza, “attacked more particularly the nerve centres” based on the “very pronounced nerve sequelae observed.” He observed many cases of depression, neurasthenia, neuritis, “and other ills which could only be described as ‘nervous’” in patients recovering from purported influenza infections.

In the discussion of his findings, W. H. Hamer, argued that the temporal relationship between outbreaks of influenza and cerebrospinal fever (meningitis), poliomyelitis, and polio-encephalitis were more than coincidence [7]. He cited his own personal observations from the period between 1914 and 1918. He observed that, although rare, neurological manifestations appeared shortly following the outbreaks of influenza infection.

A. Abrahams commented on his laboratory findings in the 1918 flu). He noted that “despite the frequency with which delirium has been met we had no single case of meningitis, although the cerebrospinal fluid was specially investigated in a number of cases [6].” Additionally, B. H. Spilsbury also published his pathological findings from central nervous system tissue [2]. “In the central nervous system there were degenerative changes in the nerve cells in several cases, especially in the cells of the motor nuclei in the pons, in some of which chromatolysis and pigmentation were found...There was general congestion of the brain...[but] no inflammation in the brain or meninges.”

Many occurrences of neurological sequelae of influenza came to light in the years following the 1918 flu outbreak. In 1920 D.J. Wood reported on two cases in the British Journal of Ophthalmology noting accommodation deficits [8]. He described two patients who, prior to the influenza epidemic, had normal vision. These patients experienced a rapid decline in their visual acuity following their bouts with flu-like illnesses. As in many other influenza-related neurological illnesses, Wood’s patients fully recovered from the cycloplegia, and paralysis of the ciliary eye muscles.

Encephalitis lethargica (EL) with its post-encephalitic Parkinsonism has been closely associated with the 1918 flu pandemic [9]. Chronicled in 1917 by Constantin von Economo in his paper “*Die Encephalitis lethargica*”, the disease was characterized by high fever, ophthalmoplegia, mental confusion, and lethargy [4, 10]. An epidemic of EL coincided with, and lasted for a decade following the 1918 influenza outbreak. Although the 1918 flu was believed to be a cause EL, its exact viral etiology has not be identified. Approximately 75% of the cases presented with ocular findings. The lethargy lasted from several days to a few months, and frequently culminated in coma and death secondary to respiratory failure [4]. About 80% of the patients who recovered from EL went on to develop a Parkinson’s-like disease [4, 11]. The Parkinsonian features described included tremor, bradykinesia and masked facies [12]. The disease was named post encephalitic Parkinson’s disease (PEP). Although the connection is controversial, research has shown that individuals who were

born between 1888 and 1924, and thus were born or were young at approximately the time of the pandemic, had a two to three fold higher risk of developing Parkinson's disease, than those born outside of that range [12].

In 1963 Poskanzer and Schwab came out with a paper which investigated the shift in the age group of patients being diagnosed with PD. They performed a cohort analysis of all cases of PD that presented to Massachusetts General Hospital and the Parkinson's Clinic from 1875 through 1961. They believed that the increase in PD diagnosis in the older population was secondary to that population being young during the outbreak of EL. They determined that cohort responsible for the rise in PD cases was between the ages of five and 59 in 1920. Based on their data, they predicted that as that cohort died off there would be a decline in the number of PD cases. They stated, "It appears that a precipitous drop will occur prior to 1980 in the number of cases." [Poskanzer]. Their hypothesis did not come to fruition as demonstrated by epidemiological data gathered by Dorsey et al. According to their report on PD in the world's most populous countries, the prevalence of PD has grown and will continue to grow; even in the absence of an neurovirulent influenza pandemic [13].

The 1950s saw transiently increased incidences of amyotrophic lateral sclerosis (AML) and "parkinsonism-dementia" on the Island of Guam [15]. In a 1987 discussion, C. P. Maurizi proposed that the pandemic of 1918 was responsible for this increased incidence. He hypothesized that evolutionary bottlenecking of the small island population left the natives with a genetic predisposition to the development AML and PEP after infection with the neurovirulent 1918 flu. In support of his argument Maurizi cited the discovery of a link between the presence of the HLA-B14 antigen and the development of PEP, suggesting that HLA-B14 was more common in the Guam population. By the 1960s, AML and PEP were on the decline in Guam [15]. It is now known that a syndrome of parkinsonism, ALS and dementia occur on Guam, and that this syndrome is not due to influenza [3].

Recent research has shed more light on the neurovirulence of the 1918 flu [10]. Tissue samples from patients suffering from the 1918 flu, EL and/or PEP were preserved and archived, and have been available for contemporary researchers to analyze the virus' effects on the CNS [16]. There has been conflicting evidence about influenza's ability to enter the CNS. Gamboa et al. were able to detect viral antigens in the brain tissue of PEP patients via immunofluorescence [12]. Whereas, McCall et al., were unable to detect viral RNA in the brain tissue of patients suffering from EL or PEP using RT-PCR [16]. A two-hit hypothesis has been proposed where either direct viral invasion (less likely) or a CNS cytokine storm caused by the virus (more likely) predispose patients to the development of PD. According to this hypothesis the brain would require a second hit (environmental, genetic etc.) later in life. The two-hit hypothesis does not require the virus to be present at the time when the patient develops EL or PEP.

After the initial pandemic, the H1N1 virus of 1918 underwent antigenic drifting, resulting in seasonal epidemics, without another major pandemic reported until the 1950s [6]. In 1957 influenza H2N2 appeared in the human population, and seemed to supplant the H1N1 strains. It resulted in the "Asian flu" pandemic [6].

In 1958 Kapila, et al. published a paper in the British Medical Journal describing the neurological disorders they observed during influenza outbreaks (documented in military bases in southern India [17]). They noted that, while the majority of flu cases had the typical clinical presentation, several cases revealed signs of neurological sequelae. They reported that 30 of 9,459 (0.3%) cases of influenza admitted to military hospitals reported neurological issues. The British military had previously evaluated two to three cases of encephalitis per year, but during the pandemic of 1957, approximately 30 cases presented per base. The doctors carefully characterized the clinical features of neurological disease in these cases, describing that “after an attack of influenza the patient was afebrile and progressing well, when suddenly there was an onset of severe persistent vomiting followed very soon by delirium, boisterousness, and coma. Some of the cases had convulsions. In a few, localizing neurological signs were noted.” The localizing signs included extensor plantar responses, and weakness and paralysis of various muscle groups, including the respiratory musculature. Thirteen patients fully recovered and 17 [out of 30] patients died. It was notable that the severity of the neurological illness did not correlate with the final outcome [17].

In their search for the cause of neurological manifestations, Kapila and his group, examined patients’ blood, urine and CSF, and performed autopsies on 17 patients from the military bases [17]. They also obtained CSF samples from eight patients who survived. They discovered serum bilirubin was elevated in 10, however the levels in most of these cases were only slightly greater than normal. CSF studies from 25 cases were within normal limits. They successfully isolated influenza A from the brain of one patient. To rule out several known infectious causes of encephalitis, they performed hemagglutinin inhibition and complement-fixation tests on four samples. Gross inspection of the brains revealed, “moderate to severe congestion with petechial haemorrhages in the white matter in all cases.” Microscopic inspection revealed, “diapedesis of cells into the Virchow-Robin space...and neuroglial proliferation,” and in the one case from which influenza A virus was isolated from the brain, “neurone degeneration, including satellitosis and neuronophagia.” Based on the presence of the antecedent influenza illness, the negative investigation for other infectious causes of encephalitis, and the non-compelling evidence for a hepatic source of the neurological derangements, the doctors concluded that they had observed a new encephalitic syndrome, and that the influenza virus was the likely causative agent [17].

Reports of neurological complications of the 1957 influenza pandemic also came from England and Wales [18]. A clinical presentation emerged and included severe headache, declining levels of arousal, coma, meningeal signs, upper-motor-neuron signs, and abnormal EEGs. Again, the CSF studies in these cases were normal or revealed only a slight elevation in lymphocytes [17]. There were sporadic reports of “organic dementia”, delirium, and Guillain-Barré-like syndromes appearing at various intervals following influenza infection. Because there were so few cases with neurological manifestations, and because the cases of influenza were diagnosed without laboratory confirmation, it was difficult to confirm a causal relationship between influenza infection and neurological sequelae [18].

Influenza A subtype H3N2 emerged in 1968, and resulted in what became known as the Hong Kong flu pandemic. This pandemic lasted until 1970 [19]. A report in the British

Medical Journal highlighted some of the neurological syndromes observed during the pandemic [20]. It listed painful amyotrophy, acute flares of multiple sclerosis (in patients who had been previously in remission), encephalitis, encephalopathy, myelopathy and a GBS-like syndrome as complications of influenza infection. The authors then described potential theories as to how the virus may have affected the nervous system [20]. An acute encephalitic syndrome was thought to be caused by direct viral invasion of the brain, and additionally it was thought to be at least indirectly responsible for syndromes such as encephalopathy, myelopathy and peripheral neuropathy. These authors confirmed, as their predecessors had described, normal CSF examinations [20].

C.E.C. Wells reported on the neurological syndromes he observed during the Wales flu epidemic which occurred from 1969 to 1970 [21]. He examined 19 cases of reported neurological disease that appeared to be preceded by an influenza-like illness. All cases presented to the Cardiff Royal Infirmary and to St. David's Hospital, Cardiff, Wales. The syndromes included encephalopathy, myelopathy and polyradiculopathy (or a combination thereof). Wells tested each patient for influenza A virus, adenovirus, and herpes zoster to confirm that the cases were truly influenza. Eight of 19 patients were confirmed as having influenza A infection. The proof of a causal relationship between influenza infection and the neurological sequelae, however, remained elusive [21].

Seven months after Wells published the aforementioned case reports on the neurological complications of influenza, he presented nine cases of influenza vaccine-associated neurological illness [22]. At that time, mass influenza vaccination programs did not exist, and vaccination was reserved for high risk groups [23]. The first case described a 23 year old man who presented with a Guillain-Barré-like picture 29 days after vaccination with a saline suspension of inactivated A and B viruses (emulsified in mineral oil) [22]. The patient had flaccid paralysis up to his thorax as well as constipation and dysuria. His CSF contained 30 WBC/mL and had 40 mg protein/100mL. The patient was able to walk again within a week, and at follow-up seven months later the only signs of the illness were sluggish patellar and ankle reflexes. Wells described eight more cases, and these included polyneuropathy, encephalopathy, bulbar paralysis, transverse myelopathy, radiculopathy and paresthesias. The onset of these presentations ranged from two hours to two weeks following vaccination. Although Wells could not prove a causal relationship between the vaccination and the neurological manifestations, he used these cases to argue against mass influenza vaccination.

The 1976 discovery of a novel H1N1 strain, which infected soldiers at the Fort Dix army base, compelled government health organizations, namely the Centers for Disease Control and the Department of Health, Education and Welfare, to embark on a massive influenza vaccination campaign. Their efforts were aimed at avoiding a devastating pandemic [23]. Although the pandemic never materialized, 40 million Americans were vaccinated under the Swine Flu Program. Fraught with problems, the program was abruptly terminated after several cases of post-vaccination Guillain-Barré syndrome were reported. At that time researchers estimated that the case rate of GBS was one in 100,000 to 200,000 vaccinations [23]. The mechanism for vaccine-associated GBS was probably molecular mimicry of the P2 protein of peripheral nerve myelin by the viral NS2 protein [10]. Normally this protein would have been removed from the vaccine, but it contaminated in several batches. There

have been no reported cases of influenza vaccine-associated GBS since the Swine Flu Program of 1976 [10].

Researchers at the University Hospital of Wales noticed an increased incidence of sub-arachnoid hemorrhage (SAH) during the 1978 flu season [24]. The number of cases had increased significantly when compared to the flu season of 1977. They proposed an association between SAH and influenza A infection. In 1978 they obtained the sera from 25 patients presenting with SAH. To test their hypothesis, they performed complement fixation assays for 14 viruses including influenza A, B and C. They compared these patients to two control groups. The researchers described a significant association between SAH and influenza A infection. They offered a few explanations, including virus-induced atherosclerosis, and a potential relationship between smoking and vascular disease lending susceptibility to influenza infection. There have been no further studies supporting this hypothesis to date, but there was one by Timmons et al. that demonstrated a lack of association between SAH and influenza infection [25].

Physicians from the University of Helsinki and the Central Public Health Laboratory in Helsinki, reported four cases of post-influenza encephalitis during the 1979-80 epidemic of the H3N2 virus [26]. They noted that there had been few reports of post-influenza encephalitis since the 1957 pandemic, but that the number of cases had been rising in the years leading up to their report. Their first case was a man who became febrile and delirious seven days after coming down with flu-like symptoms. Other than being stuporous and possibly aphasic, his neurological examination was normal. His CSF revealed a lymphocytic pleocytosis and an elevated protein level. His EEG showed generalized slowing. The physicians were concerned about HSV encephalitis, so a brain biopsy was obtained, but was negative for the presence of viral infection. The patient recovered from his delirium a day later. Serial neuropsychological tests revealed a marked improvement in the patient's memory and thinking over the course of a few weeks. His EEG returned to normal (apart from changes secondary to brain biopsy) six weeks after his initial presentation. The other three cases followed a similar course. Two cases experienced coma, and one experienced convulsions, localizing signs and relapses of delirium and coma during recovery. All four cases exhibited full recovery, and all sufferers were able to return to work. They theorized that the increase in cases of post-influenza encephalitis during the 1979-80 epidemic was more likely due to the increased incidence of influenza infection during that season, rather than the specific strain of virus responsible for the epidemic [26].

In the past two decades the Japanese have suffered an unusual amount of influenza-associated acute encephalitis and encephalopathy [27]. A national cross-sectional survey, commissioned by the Japanese Ministry of Health and Welfare, was conducted during the flu season of 1999. Kasai et al. reported 217 cases of influenza-associated encephalitis/encephalopathy. An acute encephalitis or encephalopathy was defined as occurring while the patient is still experiencing the initial viral syndrome. Children less than five years old accounted for 82.5% of those cases [28]. The clinical findings measured in this study were hyperpyrexia, unconsciousness, convulsion, headache and fatigue. The authors noted that Reye's syndrome accounted for only two of the 217 cases. They also noted that none of cases had been vaccinated for influenza.

Following each of the flu seasons from 1994 to 1995, Togashi et al. investigated all pediatric cases of encephalitis or encephalopathy, occurring on the island of Hokkaido [29]. The group identified 64 cases of encephalitis/encephalopathy, 34 (53.1%) of which were influenza associated. The 30 remaining cases were ‘strongly suspected’ of being influenza associated, given the cases’ close contact with known influenza carriers. None of the cases received the influenza vaccine, nor had they taken aspirin (thus making Reye’s syndrome highly unlikely). Of all the cases of encephalitis/encephalopathy 100% had fever and unconsciousness, 79% had convulsions, 82% had EEG abnormality, 73% had CT abnormality, 64% had MRI abnormality and 29% had a CSF pleocytosis. Twenty-eight of 64 patients died, 13 had permanent neurologic sequelae, and 23 recovered completely. The most common CT findings were “symmetric low-density intensities extending from the thalamus to the brainstem”. Those lesions seemed to correlate with the more detailed MRI findings. The authors noted that there had been very little evidence in the past for direct viral invasion of the CNS in cases of acute encephalitis/encephalopathy. They emphasized, however, that the acute cases differed greatly from the likely immune-mediated postinfectious encephalitis. They stated in their findings that, “one striking feature of our observations is that 25 of the 28 patients who died had already been in cardiopulmonary arrest on admission, or died within a few days of the onset of fever...This fulminant clinical course may suggest that the direct invasion of the CNS by the virus plays a major role in the pathogenesis of brain dysfunction in these patients”. The authors used their findings to make the case for improving the vaccination rates among Japanese children [29].

From approximately 2005 through 2006 avian influenza A, H5N1, spread around the world and threatened to rival the pandemic of 1918 [30]. In a 2006 paper, Kristensson, discussed the neuropathological features of earlier H5N1 viral infections and prognosticated the potential neurological complications of the looming pandemic. He cited the 1997 Hong Kong outbreak of H5N1. Two out of four isolates from the 1997 Hong Kong strain (which could pass directly from birds to humans) were found to be neurotropic in mice [30].

Improvements in technology have allowed researchers in recent decades to reinvestigate the connection between influenza, EL and PD. Takahashi et al. performed intracerebral inoculation of mice with influenza A strains known to be neurovirulent [31]. The group then evaluated the mice for clinical signs of Parkinsonism and examined the brain tissue for regional presence of the virus. On clinical examination the mice showed decreased movement, weight loss, hyperirritability, tremulous movements and convulsions. On histopathological examination, viral antigens were discovered in the neurons of the hippocampus and the dopaminergic neurons of the substantia nigra. The researchers concluded that the substantia nigra could be a major target for neurovirulent forms of influenza A virus in humans as well; possibly causing PD [31].

Studies of animals infected by H5N1 in the wild, including birds and waterfowl, revealed a disease complex that included behaviors consisting of abnormal postures, imbalance, and the inability to initiate movement; symptoms that appeared to mimic those seen in Parkinson’s disease. Examination of the brains of those birds showed a diffuse gliosis and evidence of degeneration of the brainstem and midbrain (Smeyne, unpublished data). To investigate if this virus was capable of inducing a similar pathology in mammals, C57BL/6 mice were

intranasally inoculated with A/VN/1203/2004 H5N1 (to mimic the normal route of infection of influenza virus), after which the presence of virus was examined in all three divisions of the nervous system (ENS, PNS and CNS). H5N1 virus first infected neurons located in the enteric nervous system and then traveled through peripheral nerves (likely the vagus, innervating gut and lung) into the CNS. The first nucleus to be infected was the dorsal motor nucleus of X and the solitary nucleus; each primary sites of innervation of the vagus nerve [32 - 33]. Once in the CNS, the virus appeared to infect neurons and microglia, without any obvious infection of astrocytes. As the infection spread through the CNS (starting at 3 days post infection (dpi), progressing over the next 7 days from the brainstem rostrally into the midbrain, and eventually into the cortex. A second route of entry into the brain likely occurred through the olfactory nerve into the olfactory bulb of the brain that was observed after 3 days but before 7 dpi. No matter what the origin or direction of the CNS infection, active H5N1 infection in the CNS was absent by 21 dpi, although there appeared to be a persistent microglial activation that lasted beyond 60 days dpi.

Although there was clear localization of the H5N1 virus in CNS structures shown to degenerate in Parkinson's disease [30], Jang et al., sought to empirically determine if the virus could induce a Parkinsonian pathology. Several parameters were examined, including loss of dopaminergic neurons in the SNpc, loss of dopamine in the striatum, and induction of aggregated phosphorylated alpha synuclein. They found that shortly after H5N1 infection in the CNS, the animals appeared transiently bradykinetic with a distinguishable tremor; symptoms that disappeared by 21 dpi when virus was no longer detected in the CNS. Examination of the SNpc of infected animals showed a small but significant loss of tyrosine-hydroxylase positive dopaminergic neurons that persisted through 60 dpi. Similar effects were seen in dopamine levels in the striatum. Infection with H5N1 also induced a persistent and seemingly permanent upregulation of phosphorylated alpha-synuclein in all regions infected by H5N1. This appeared to be a specific effect of the virus since areas of the brain that were not infected did not show altered phosphorylated synuclein levels [3].

Researchers at the University of British Columbia Hospital Movement Disorders Clinic noticed that teachers and health care workers accounted for an inordinately large proportion of their PD patients [34]. Given the growing body of evidence for viruses as etiological factors in the development of PD, Tsui et al hypothesized that an increased exposure to viral respiratory infections, including influenza, predisposed these workers to the development of PD. Employing a case -control design, where the cases were all 414 PD patients seen at the clinic between 1986 and 1994; they found that PD was associated with being a teacher as well as working in the health care field [34].

From the Spring of 2009 through the Spring of 2010 the world encountered a novel influenza A, subtype H1N1, commonly referred to as Swine Flu. Cases of H1N1 influenza A first appeared in April of 2009 [35]. By May 2009 the CDC received its first case reports of neurological complications [36]. The Dallas County Department of Health and Human Services identified four patients who suffered from neurological illnesses after contracting the Swine Flu. All of the cases were children, who ranged in age from 7 to 17 years. The first case was a 17 year old boy who presented to the emergency department with one day of fever reaching a peak of 102.6°F. He was diagnosed with influenza A by a rapid enzyme

immunoassay, and he was discharged on oseltamivir. The following day he experienced generalized weakness, disorientation and slow mentation, and returned to the ED. The CT scan of his brain was normal, as was his CSF profile. He was admitted, and continued on the oseltamivir. On the third day of illness, the patient's mental status returned to normal and he regained his strength. He completely recovered from his illness without sequelae.

The second patient, experienced encephalopathy and three seizures, four days after the onset of an influenza-like illness with fever. The inpatient work-up revealed a normal MRI, a normal CSF profile and an EEG that was consistent with encephalopathy. He was treated with antiviral medications, and he returned to his baseline neurological status seven days after admission, and he had no neurological sequelae. The third case was similar to the second, except that the patient had a MRI notable for 'nonspecific white matter abnormalities that were not characteristic of infection or inflammation,' and also localized abnormalities on EEG. The final patient's history was notable for ingestion of 81mg of aspirin, a known risk factor for developing Reye's syndrome [10]. His neurological manifestations included ataxia, disorientation, visual hallucinations and a seizure, and consisted of 'episodic eye rolling and tongue thrusting.' He had a normal head CT, and an EEG consistent with encephalopathy. Like the other cases, he completely recovered within a few days [36].

For more than a century physicians and researchers have been aware of neurological illness associated with influenza (summarized in Table 1), but a causal link has been difficult to prove. In the case of Parkinson's disease this is typically due to the significant number of years between the influenza symptoms and the initiation of Parkinsonian symptoms. As discussed in regard to the H5N1 viral infection, as well as descriptions from examination of cases of von Economo's encephalopathy [37], one of the more interesting findings was the persistent activation of microglia, the resident immune cells of the CNS, seen only in regions of the brain infected by influenza [3]. Long-term activation of the CNS is not unique to CNS infection since other insults, including those that induce Parkinsonism, have shown persistent microglial activation [38-40]. One of the hallmarks of immune cells is their "memory" which allows for a rapid, a sometimes overwhelming, response should a second insult occur [41-43]. Thus, an early exposure to an agent that might have subclinical symptoms, could prime the CNS to react to a later insult or series of insults that would normally not elicit any pathological response. This mechanism for generation of pathology has been termed the "hit and run" theory [44, 3].

Epidemiology has shown that the greatest risk factor for developing Parkinson's disease is age [45, 46]; and the typical onset occurs at around 55 years of age. It is not out of the realm of possibility that Parkinson's disease may develop as a sequela of numerous small "hits" (which may include influenza) that occur over the course of a lifetime. With improving techniques for identifying influenza virus infection, diagnostics for detailing neuroinflammation, and a newly "refound" awareness of the potential roles of virus in the development of Parkinson's disease, it is likely that further mechanistic studies will allow for development of novel treatments that could prevent or delay onset of Parkinsonian symptoms.

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Table 1

by Julia Henry

Year of Pandemic* or Epidemic#	Virus	Reported Neurological Manifestations	References
1898	H3N2		4
1918	H1N1	delirium, cycloplegia, encephalitis lethargica,	1, 2, 4, 5, 6, 7, 8, 11,12
1957	H2N2	encephalitis, seizures, muscle paralysis, GBS	17, 19
1968	H3N2	amyotrophy, MS flares, encephalitis, encephalopathy, myelopathy and GBS	20
1969 Wales	Unknown	encephalopathy, myelopathy, polyradiculopathy	21
Vaccine 1969 Wales	Unknown	GBS, encephalopathy, bulbar paralysis, transverse myelopathy, radiculopathy, paresthesias	22
Vaccine 1976 United States	H1N1	GBS	23
1977	H1N1	Unknown	Unknown
1978 Wales	Unknown	SAH (questionable)	24, 25
1979 Finland	H3N2	encephalitis, seizures, relapsing delirium	26
1994 - 1995 Japan	H1N1 and H3N2	encephalitis, encephalopathy, seizures	28, 30
1997 Hong Kong	H5N1	laboratory discovery of viral neurotropism in animals	30
2001 Hong Kong	H5N1	laboratory discovery of viral neurotropism in animals	30
2006	H5N1	Unknown	30, 32
2009	H1N1	encephalopathy, seizures, ataxia	35

* Pandemics listed in bold

Epidemics listed with their location