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H1N1 INFECTION AND ITS NEUROPSYCHIATRIC ASSOCIATIONS

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ABSTRACT
Influenza is a viral infectious disease commonly referred as 'flu'. Humans develop the swine flu infection when they are closely associated with pigs (for example, farmers, pork processors), and likewise, pig populations have occasionally been infected with the human flu infection. The 2009 H1N1 influenza virus was first detected in people in the United States in April 2009. More recently in 2015, a mutant strain of H1N1 which caused the global pandemic in 2009, spread across India with over 10,000 reported cases and 774 deaths. Acute neurological manifestations have been reported during epidemics and are often consistent with serious sequelae or death. The other neurological complications are seizures, Reye's Syndrome (RS), acute necrotizing encephalopathy, transverse myelitis, and aseptic meningitis as well as autoimmune conditions, such as Guillian-Barre Syndrome (GBS). The psychiatric complications include depression, mania, bipolar disorder, schizophrenia and dementia.

KEYWORDS: Influenza, Swine flu, Epidemiology, Neurological complications, Psychiatric sequelae, Treatment.

INTRODUCTION

Influenza is a viral infectious disease commonly referred as 'flu'. Influenza viruses are RNA viruses and belong to the family 'orthomyxoviridae' with three genera: Influenza Virus A, B and C.[1] The virus infects the respiratory tract of pigs and can be transmitted to humans either by inhaling the Infected droplets present in the air through coughing or sneezing or by touching contaminated surfaces followed by mouth or nose. The virus was first isolated from pigs in 1930 in the U.S. and has been recognized by pork producers and veterinarians to cause infections in pigs worldwide.[2] The virus can last about one to two weeks in pigs that survive. Symptoms include influenza-like illness like cough, sore throat, fever, nasal discharge, watery eyes, abdominal pain etc. Humans have developed the swine flu infection when they are closely associated with pigs (for example, farmers, pork processors), and likewise, pig populations have occasionally been infected with the human flu infection. In most instances, the cross-species infections (swine virus to man; human flu virus to pigs) have remained in local areas and have not caused national or worldwide infections in either pigs or humans.

It has been lately observed that people infected with swine flu show some unusual behavior like uncontrolled hand washing, fear of public places etc. This article will review the available literature on swine flu and its possible association with psychiatric disorders.

HISTORY

The outbreak of Influenza occurred prior to the isolation of Influenza virus. It was first isolated in 1930 by retrospective serologic survey of individuals alive during those years.

Major influenza outbreaks.

YEARS	SUBTYPE	EXTENT OF OUTBREAK
1889-1890	H2N8	Severe pandemic
1900-1903	H3N8	Moderate pandemic
1918-1919	H1N1	Severe pandemic
1933-1935	H1N1	Mild pandemic
1946-1947	H1N1	Mild pandemic
1957-1958	H2N2	Severe pandemic
1968-1969	H3N2	Moderate pandemic
1977-1978	H1N1	Mild pandemic
2009-2010	H1N1	pandemic

The most severe influenza pandemic was detected in 1918 with estimated 50 million deaths or more the highest mortality rate of any disease outbreak in the recorded history.[3]

The 2009 H1N1 influenza virus was first detected in people in the United States in April 2009. This virus was originally referred to as "swine flu" because laboratory testing showed that its gene segments were similar to influenza viruses that were most recently identified in

and known to circulate among pigs. According to CDC this virus resulted from reassortment, a process through which two or more influenza viruses can swap genetic information by infecting a single human or animal host. When reassortment does occur, the virus that emerges will have some gene segments from each of the infecting parent viruses and may have different characteristics than either of the parental viruses. In this case, the reassortment appears most likely to have occurred between influenza viruses circulating in North American pig herds and among Eurasian pig herds. Reassortment of influenza viruses can result in abrupt, major changes in influenza viruses, also known as "antigenic shift." When shift happens, most people have little or no protection against the new influenza virus that results.[4]

It is not known when reassortment occurred to create the 2009 H1N1 influenza virus. Testing of the virus suggests that this reassortment event may have occurred years prior to the first reports of 2009 H1N1 influenza infection in people.[4] Scientists call 2009 H1N1 influenza a "quadruple reassortant" virus, because although each separate gene segment of the virus has been found in pigs previously, the individual gene segments of the virus originated from humans, birds, North American pigs and Eurasian pigs.

Pigs can be infected by influenza viruses found in birds and other animals as well as people at the same time, Therefore, pigs represent a mixing vessel in which influenza viruses from different species can swap genes. For at least 80 years, influenza viruses known as "classical swine H1N1" viruses have circulated in North American pigs. However, in the late 1990s, a series of reassortment events occurred between influenza viruses found in pigs, humans and birds. As a result, swine influenza viruses with genes from humans, North American pigs and birds have existed in many parts of the world for around 10 years prior to 2009 H1N1 flu. Mixing of these "triple reassortant North American swine influenza viruses" with Eurasian swine viruses likely resulted in the 2009 H1N1 influenza virus.

EPIDEMIOLOGY

Swine flu was first isolated in the 1930 by researchers in the United States from pigs and it was subsequently recognized by pork producers and veterinarians as a cause of flu infections in pigs. People who are closely associated with pigs have been known to develop an infection, and pigs have also been infected with human flu from these handlers. In the vast majority of cases, cross-species transmission of the virus had remained confined to the specific area and not caused national or global infections in either pigs or humans. Unfortunately, due to the potential for genetic variation in the swine flu virus, there is always a possibility for cross-species transmission with the influenza viruses to occur.

The 1918 deadly influenza pandemic caused by H1N1 influenza virus, infected approximately 500 million people around the world and caused the death of roughly fifty to a hundred million people. The H1N1 variant of swine flu is the progeny of the strain that caused the 1918 swine flu pandemic. Although persisting in pigs, the descendant variants of the 1918 virus have also known to infect humans, contributing to the yearly seasonal epidemics of influenza. Direct transmission of the virus from pigs to humans is a rare occurrence, with only 12 documented cases in the United States since 2005. The potential retention of influenza virus strains in swine after these strains have disappeared in the human population, essentially make pigs a reservoir where swine influenza viruses could persist, and later emerge to reinfect humans once their immunity to these strains has waned.[5,6]

The "2009 swine flu" strain, originated in Mexico. It was termed novel H1N1 flu since it was mainly found infecting humans and exhibits 2 main surface antigens, hemagglutinin type 1 and neuraminidase type 1. The 8 RNA strands in novel H1N1 flu have 1 strand from human flu strains, 2 derived from avian (bird) strains, and 5 that were derived from swine strains. The infection spread fast around the world and on June 11, 2009, the World Health Organization (WHO) declared the global influenza A (H1N1) pandemic, the first one of the 21st century. The pandemic H1N1 became the dominant influenza strain in 2009. During the 2009 pandemic, the Centers for Disease and Control and Prevention (CDC) estimated that there were 43 to 89 million cases of swine flu reported during a 1-year span, with 1799 deaths in 178 countries worldwide.[7,8]

However, most of the cases were mild and self-limiting and mortality was not as high as estimated. By the end of the pandemic (August 10, 2010), at least 18,448 laboratory-confirmed deaths were reported by the WHO as associated with the new virus strain.[9]

In 2011 an outbreak of new swine flu virus known as influenza A H3N2v (commonly termed H3N2v) occurred. The "v" in the name means the virus is a variant that normally infects only pigs but has begun to infect humans. There have been small outbreaks of H1N1 influenza since the pandemic 2009.[2]

More recently in 2015, a mutant strain of H1N1 which caused the global pandemic in 2009, spread across India with over 10,000 reported cases and 774 deaths.

Many researchers now consider that two main series of events could have led to swine flu and also avian or bird flu becoming a major cause for influenza illness in humans.

Various combinations of RNA segments can result in a new subtype of virus (this process is known as antigenic shift) that may have the ability to preferentially infect humans but still show characteristics unique to the swine influenza virus. It is even possible to include RNA

strands from birds, swine, and human influenza viruses into one virus if a single cell becomes infected with all three types of influenza (for example, two bird flu, three swine flu, and three human flu) RNA segments to produce a viable eight-segment new type of flu viral genome. Formation of a new viral type is considered to be antigenic shift; small changes within an individual RNA segment in flu viruses are termed antigenic drift and result in minor changes in the virus. However, these small genetic changes can accumulate over time to produce enough minor changes that cumulatively alter the virus' makeup over time (usually years).

MORPHOLOGY OF INFLUENZA VIRUS

Influenza viruses are member of Orthomyxoviridae family and consist of three genera: A, B and C. They are spherical in shape 80-120 nm in size. The viruses comprise of a helical nucleocapsid surrounded by an envelope. The envelope had two surface antigens, Hemagglutinin (HA or H) and Neuraminidase (NA or N). Hemagglutinin, which is the major projection on the influenza virus surface, binds to the host cell receptors and promotes the fusion between the virus envelope and the host cell, whereas neuraminidase is responsible for the release of progeny viruses by cleavage of the terminal sialic acid.[10] The influenza virus A has 16 different types of hemagglutinin (H1−H16) and 9 different types of neuraminidase (N1−N9). Recently, a novel type of hemagglutinin (H17) was identified in bats. Based on the combinations of hemagglutinin and neuraminidase types on the cell surface, the viruses are classified in diverse subtypes such as H1N1, H3N2 or H5N1.[11] Pigs are considered as the mixing vehicles for different subtypes.[12]

The core of influenza viruses contains a negative sense single stranded RNA genome that is composed of eight separate gene segments.[10] Two types of mutations can occur within the genome. First, an antigenic drift those are point mutations within the genome causing mild changes in the surface antigens and thus creating a new variant of an existing strain. Second, an antigenic shift that is a new recombination of gene segments which can occur when a host is infected with influenza viruses from different species (human, birds, pigs), leading to a formation of a completely new strain.

Transmission of Swine flu virus occurs from person to person by inhalation or ingestion of droplets containing virus from people sneezing or coughing; it is not transmitted by eating cooked pork products.

INFECTION CONTROL MEASURES IN INFLUENZA VIRUS

Transmission or occurrence of disease from Influenza virus can be prevented by using appropriate infection control measures. In developing and resource constrained countries, pharmacological interventions such as vaccines and antivirals do not play a major role in control of influenza virus, due to limited supply, lack of access and the high costs involved. Such countries will have to depend on various general preventive measures to control influenza virus. General preventive measures include the use of personal protective measures such as- covering of mouth and nose while coughing or sneezing, frequent hands washing with soap and water, avoidance of overcrowding and isolation of symptomatic individuals. Patients should be kept in isolation room or cohorting of the same disease patients can be done. For containment of cough and sneezes use of personal protective equipment such as gloves and mask for staff and patients can be done. Hand hygiene, if done properly is effective in preventing various respiratory viral infections.

Vaccines for the prevention of influenza virus are also available in various countries. Both Inactivated (Injectable) and live attenuated vaccines (Intranasal spray) are available for influenza virus. Injectable vaccines are most commonly used vaccines. Injectable vaccines are given as single dose by intramuscular route except for 6 months to 8 years of age where two doses are required 4 weeks apart. Immunity last for 6-12 months and efficacy of vaccine varies from 25-67%.

Antivirals are also available in limited supply, and should be used cautiously as they have their own side effects. If the likelihood of complications is low, antiviral chemoprophylaxis should not be given to individuals at risk for infection or to healthcare workers. If the likelihood of complications is high (either due to the strain or baseline risk of the exposed group), oseltamivir or zanamivir may be used as postexposure chemoprophylaxis for affected individuals, especially healthcare workers.[13]

NEUROLOGICAL COMPLICATIONS AND PSYCHIATRIC ASSOCIATION OF INFLUENZA VIRUS

The reports of influenza-associated acute neurological syndromes are available from 1985 onwards.[14-16] Acute neurological manifestations have been reported during epidemics and are often consistent with serious sequelae or death. An increased incidence of influenza-associated encephalitis/encephalopathy (IAE) has been reported in Japan, mainly in children. Other acute clinical neurological manifestations include seizures, Reye's Syndrome (RS), acute necrotizing encephalopathy, transverse myelitis, and aseptic meningitis as well as autoimmune conditions, such as Guillian-Barre Syndrome (GBS), which may occur during the course of influenza infection.[17-19] There is evidence that influenza can directly lead to acute encephalitis.[20] In recent times, a range from mild encephalitis to motor disturbances to coma has been reported with H5N1 infections in poultry and in humans. Influenza-related neurological complications are rare in immune-competent adults with variable clinical signs and pathology. These complications have been reported sporadically in the literature over the past 60 years. In these series, a subset

of patients (both children and adults) developed a newly described entity termed "acute necrotizing encephalopathy" (ANE).[21] Many patients with this syndrome present with high fever, seizures, and alterations in mental status that rapidly progress to coma. Brain imaging often demonstrates symmetric white matter, thalamic, basal ganglia, and/or pontine involvement. Neuropathological studies on autopsy tissue show necrosis in these areas, and the lesions are often associated with punctate hemorrhages. Permanent and severe disability or death often result. ANE has been associated with several viruses, but influenza viruses seem to be the most common infectious agent.[21] Another neurologic manifestations of influenza known to occur includes acute disseminated encephalomyelitis (ADEM).

The pathogenesis of neurological complications is not well understood and has not been elucidated so far. It is most likely caused by a para- or post- infectious immune mediated mechanisms rather than direct viral invasion of the brain and the spinal cord.[22]

This mechanism is well supported by several observations including absence of the virus RNA in the CSF. Another hypothesis is the correlation of the severity of some neurological complications with the concentration of pro-inflammatory cytokines. These cytokines can induce vascular endothelial injury, increase blood-brain barrier permeability, induce apoptosis of cells (both neurons and glia) and cause acute edema and necrosis involving both grey and white matter. The last observation is the occurrence of several cases of ADEM which is a well-known autoimmune demyelinating disease.[23]

Influenza virus is also associated with various psychiatric disorders. There are case reports of acute psychosis following influenza infection.[24] The acute manifestations of swine flu are simply the behavioral reactions, misdiagnosis/over-treatment and other acute neurological manifestations. In a nationwide cross-sectional telephonic survey of 997 adult citizens of England, Scotland, and Wales after swine flu was declared as pandemic, a study group[25] found significant behavioral changes (as precautionary measures) such as following 'some recommended behavior' (increases in hand washing and surface cleaning or plans made with a "flu friend") in about 38% of participants over the past four days, and nearly 5% carried out 'some avoidance behavior' (engaged in one or more of six behaviors such as avoiding large crowds or public transport). These behavioral changes were correlated with a high level of anxiety. There is a report of misdiagnosis at the height of the fear of the swine flu pandemic even for a case of sore throat and prescribed unnecessary oseltamivir by health professionals. There is a report of bizarre neuropsychiatric behavioral changes in one adolescent with novel H1N1.[26]

Depression

A retrospective Australian study with participation of 2514 adolescents/young adults reported an increased prevalence of suicidal and depressive symptoms in people who were born during flu peak in the Southern hemisphere, in comparison with those born in the Northern hemisphere,[27] but a prospective study by influenza antibody titer disapproved this correlation.

Mania

A case of mania induced by influenza B infection has been reported with hypothesis of connection between the locus ceruleus and influenza virus.[28] Another study in Europe also reported a manic psychosis in influenza.

Bipolar disorder

In comparison with bipolar disorder, a case-control study found that the risk of occurrence of uniploar affective disorders is increased in people who were exposed to an influenza epidemic during the second trimester which supports the neuro-developmental hypothesis of affective disorder.[29]

Parkinson's disease

The earlier linkage of Parkinsonism with influenza infection was reported after the 1918 influenza pandemic with observation that a number of people showed diminished mobility and other neurological symptoms suggestive of Parkinson's disease (PD). Subsequent evidence is also available for this linkage from epidemiological data and findings of the presence of Type A influenza antigens in Encephalitis lethargica (EL) patients. The lack of viral RNA from brains of post-encephalic Parkinsonian patients[30] and the absence of any known mutations of direct infection[31] are the major drawbacks in the understanding the role of influenza as a Parkinsonian agent.

In a recently published animal study[32] elevated levels of alpha-synuclein, loss of 17% dopaminergic neurons in the substantia nigra and persistent inflammation in areas of the brain infected with H5N1 influenza strain have been reported. All experimental mice developed tremors and movement difficulties suggestive of PD. However, there is no report of PD in human survivors of the H5N1 flu so far and it is too early to know whether those infected are at an increased risk as only a few years have passed since the report of the first cases. Researchers also acknowledge that 70% or more loss of dopaminergic neurons is required for full-blown PD to manifest and the observed 17% reduction in dopaminergic neurons alone may not be sufficient to cause PD, but it may make the brain more susceptible, especially in combination with other factors such as genetic, other environmental triggers, or simply old age.

Schizophrenia

A British study[33] first reported "mental disturbances" in 80 patients of influenza admitted in a psychiatric

hospital, of whom 16 were diagnosed with delirium, 25 with dementia praecox, 23 with "other types of psychosis," and 16 who could not be classified. He considered that the Spanish pandemic of influenza (1918) could have led to the development of dementia praecox, but neither he nor his contemporaries raised the possibility of influenza as an etiological agent for schizophrenia that could occur *in utero*.

In subsequent studies, a high prevalence of schizophrenia was documented in children born in winter and early spring that witness influenza infections.[34] Approximately 50% of studies have reported positive associations among 25 incidence studies of schizophrenia in the offspring of women who were thought to have contracted influenza during pregnancy.[35] The reliability of the documentation of exposure about maternal influenza in these studies are questionable as it is generally based on self-reports of participants or on occurrences of influenza epidemics contemporaneous with their pregnancies. To counter this problem, an American study[36] analyzed influenza antibodies in a case-control study in a population-based birth cohort (in sera drawn from pregnant women whose children later developed schizophrenia, and compared with a matched control group of women whose children did not develop schizophrenia) and found a dramatic sevenfold increase in the risk of schizophrenia among the offspring of women who were exposed to influenza during their first trimester of pregnancy, but not during the second and third trimester. The data collected from actually infected pregnant women in two studies have found no increase in risk of schizophrenia among their children Polymerase chain reaction-based studies in pregnant women have not detected influenza virus-specific nucleic acid sequences in brain tissue or CSF.[37] These evidences along with indirect evidence from animal studies suggest that human influenza viruses may have caused inherent immunological distortions in mind.[38]

Dementia and mental retardation

An Asian study[39] reported a case of progressive dementia and prolonged gait disturbance after initial presentation of delirium correlated with serologically confirmed influenza A/H3N2 infection in a 91-year-old female patient. Increased risk of mental retardation (MR) was observed in adulthood in children of prenatal exposure to Hong Kong flu[40] during the winter of 1969-70 especially in third to fourth month of gestation.

EFFECTS OF ANTIVIRAL TREATMENT

Oseltamivir, a neuraminidase inhibitor, is the most commonly used and generally well tolerated medication for swine flu worldwide and encouraging results have been observed if treated within 48 hours of detection. Oseltamivir (Tamiflu) is effective for treating both seasonal flu and H1N1 infection. Use of Oseltamivir has increased since the influenza A (H1N1) epidemic.[41,42] With the increased use of oseltamivir, psychiatric symptoms have been reported as side effects.

Between 1999 and 2007, a total of 480 million patients worldwide were administered oseltamivir, and psychiatric side effect surveys were conducted and it was found that in Japan 2,772, the United States 190, and in other countries 89 patients suffered from psychiatric illness.[43]

Psychiatric side effects were more common in infants and children aged 16 years or younger than in adults (2,218 children vs. 833 adults),[44] and generally occurred within 48 hours of receiving oseltamivir.[45,46]

Behavioral problems such as jumping and falling from balconies has been reported in young Japanese patients treated with oseltamivir[47] that lead authorities to issue warning against the prescription of oseltamivir. A case of oseltamivir-induced mania was reported in an 18-year-old Chinese lady who was admitted for H1N1 in Hong Kong with family history of bipolar disorder. There is also a report of oseltamivir-induced delirium in a geriatric patient.[48] In an internet-based cross-sectional survey,[49] 18% of oseltamivir-treated H1N1 UK schoolchildren had mild neuropsychiatric side-effects and reported one or more following symptoms: poor concentration/unable to think clearly, problems in sleeping, feeling dazed/confused, bad dreams/nightmares, and behaving strangely.

In post-marketing surveillance of tamiflu, the following transient neuropsychiatric adverse effects were reported mainly from Japan: delusions, hallucinations, sleep problems, abnormal behavior leading to injury, convulsions, encephalitis and delirium to suicide (mainly documented in teenagers). US Food and Drug Administration (FDA) suggested that the increased reports of neuropsychiatric events in Japanese children are most likely related to an increased awareness of influenza-associated encephalopathy, increased access to Tamiflu in that population, and a coincident period of intensive monitoring of adverse events. These prompted the inclusion of precautions to the US product label for oseltamivir.[50]

A retrospective cohort study[50] funded by Roche (who make Tamiflu) noted a higher rate of episodic mood disorders among those aged 17 years and below receiving oseltamivir compared to those who received no antiviral treatment.

There are many etiological mechanisms are proposed for neuropsychiatric side-effects of oseltamivir. A study hypothesized that oseltamivir carboxylase, the main metabolite of oseltamivir, has an effect on the CNS with a role in CNS development and impulse conduction. It was also found that oseltamivir increases the release of dopamine in the medial prefrontal cortex and may be the cause of abnormal behavior in young patients.[51]

Another mechanism is that oseltamivir is generally prescribed in combination with nonsteroidal anti-inflammatory drugs (NSAIDs) or antihistamine agents. The effect of interactions between oseltamivir and these agents on the central nervous system is poorly understood. The oseltamivir metabolite changes as it interacts with other drugs and may affect the central nervous system.[52,53]

Psychiatric side effects of oseltamivir have been reported more frequently in Japan than in the United States and Europe.[47] This may be explained by the extensive use of oseltamivir during the influenza pandemic in Japan; however, genetic features associated with ethnicity or geographic factors may also contribute to the higher incidence of psychiatric symptoms.

The genetic mechanism in the Japanese population may be responsible for the neuropsychiatric side-effects with oseltamivir including suicide. Clinicians are asked to closely monitor this potential side-effect of suicide in every patient, especially with a positive family or personal history of mental illness.

Controversy exists regarding whether neuropsychiatric manifestations are a result of influenza per se or side-effects of oseltamivir. A retrospective cohort study of influenza in 1 to 21 years from USA found that there was no evidence of increased risk of adverse neuropsychiatric outcomes among the study population treated with oseltamivir for influenza.[50]

Although several studies have demonstrated that oseltamivir induces psychiatric symptoms, this issue remains under debate. Further study of the mechanisms underlying the psychiatric side effects of the drug is needed. In the meantime, close observation and follow-up are recommended when oseltamivir is administered for the treatment of influenza.

Effect of vaccination on neuropsychiatric manifestation of influenza virus

There are insufficient details in the published reports about neurological complications related to influenza A (H1N1) infection or vaccination. As it is reported, the vaccine of influenza virus itself may promote an exacerbated peripheral inflammatory response,[54] the extension of which may be modulated by individual biological factors, that is, age, sex, and genetic background. Furthermore, an increased systemic or peripheral inflammatory response may promote neuroinflammation, which may underlie the neurological symptoms.[55]

In this regard, the severity of brain dysfunction even in cases with non-clinical neurological findings may be correlated with high levels of pro-inflammatory cytokines in blood and CSF (cytokine storm).[56] However, in some cases of CNS involvement, no cytokine storm or tissue inflammatory infiltrate has been found.[57] It is also possible that both the viral infection and the vaccination promote blood–brain barrier (BBB) dysfunction,[58] producing neuro-inflammation and neurological disorders. With respect to neurological diseases related to the infection, it is important to consider the higher prevalence of encephalopathy or encephalitis in the pediatric population. The size of the influenza viral particle may prevent it from crossing the barrier in adults, but an immature BBB may be prone to virus invasion.[59]

There are many reports of GBS identical to the subacute and chronic forms of polyradiculoneuropathy (very rarely) and subclinical myelopathies (a very few cases of) following vaccination for influenza. Among all these, GBS is a highly controversial side-effect in view of earlier reports of GBS due to influenza infection itself.

Probably for the first time, occurrence of GBS with vaccine for influenza outbreak was reported in 1976 during a large-scale immunization campaign in New Jersey, USA which led to a cessation of this mass immunization. An estimate suggests that there was a risk of one additional case of GBS per 100,000 people vaccinated for influenza in comparison with background prevalence of GBS of 1–2·3 per 100,000 in the general population. 'Lancet Neurology[60] observes that the chances of detecting cases of GBS during the development phase are low since the number of participants in most clinical trials of vaccines against H1N1 is unlikely to exceed 1500. In view of reports of mass vaccination in this swine flu pandemic, the timely reporting and analysis of any neurological complications during the immunization period will be essential.

However, preliminary data from CDC[4] (1 October- 24 November 2009) suggests that there are no substantial differences noted between H1N1 and seasonal influenza vaccines in the proportion or types of serious adverse events reported after FDA gave license for H1N1 vaccines on 15 September 2009. In light of the H1N1 pandemic, the WHO recommends continuation of surveillance of acute flaccid paralysis that may represent a useful means of monitoring GBS during the pandemic. In view of controversy of whether GBS is a part of influenza, or a side-effect of influenza vaccination and absence of clear evidence for either, WHO recommended collaborative active surveillance for GBS during immunization which might give better insight about the controversial etiology of GBS.

The evidences for the involvement of the brain in the pathogenesis of influenza virus are available from animal studies. A study of the immunization of rabbits with certain H1N1 influenza viruses led to production of autoantibodies to a brain-specific protein of 37kDa, present in various species including humans These autoantibodies were produced only in the brain and not in other tissues. These antibodies were not elicited by other Influenza A or B viruses. In histological studies,

the reaction with antiviral antisera was specific to gray matter and was confined to sera that recognized the 37-kDa protein. The binding of the antibody was prominent in regions comprising neuronal cell bodies in cellular layers of the dentate gyrus, hippocampus, cerebral cortex, and cerebellum and not detectable in myelin-rich regions, such as the corpus callosum. The 37-kDa protein, therefore, appears to be a neuronal antigen. Antibodies directed against this protein may be involved in the pathogenesis of one or more of the neuropsychiatric disorders that occur after infection with influenza.[61]

There are well-documented acute neuropsychiatric manifestations of influenza and swine flu like encephalitis/encephalopathy, seizures, transverse myelitis, aseptic meningitis, and GBS. Among the chronic manifestations of influenza, the evidence for schizophrenia and PD require further scientific data. Suicide and GBS are the two controversial neuropsychiatric side-effects of antiviral drug oseltamivir and influenza vaccination respectively, undergoing post-marketing surveillance.

Thus the neuropsychiatric manifestations implicated with the infection of influenza/swine flu, the relation between swine flu and neuropsychiatry, especially the chronic manifestations need to be explored further.

REFERENCES

1. Dolin R. Influenza. In: Kasper DL, Braunwald E, Fauci AS, Hauser SL, Longo DL, Jameson JL, editors. Harrisson's principles of internal medicine. 16th ed. New York: McGraw Hill, 2005; 1066–70.
2. Gibbs, Adrian J.; Armstrong, John S.; Downie, Jean C. "From where did the 2009 'swine-origin' influenza A virus (H1N1) emerge?". Virol J, 2009; 6: 207.
3. Chowell G, Echevarría-Zuno S, Viboud C, Simonsen L, Tamerius J et al. Characterizing the epidemiology of the 2009 influenza A/H1N1 pandemic in Mexico. PLoS., 2011; Med 8: e1000436.
4. www.cdc.gov/h1n1flu/information_h1n1_virus_qa.htm.
5. Kshatriya RM, Khara NV, Ganjiwale J, Lote SD, Patel SN, Paliwal RP. Lessons learnt from the Indian H1N1 (swine flu) epidemic: Predictors of outcome based on epidemiological and clinical profile. J Family Med Prim Care, 2018 Nov-Dec; 7(6): 1506-1509.
6. Nickol ME, Kindrachuk J. A year of terror and a century of reflection: perspectives on the great influenza pandemic of 1918-1919. BMC Infect. Dis, 2019 Feb 06; 19(1): 117.
7. Hasan F, Khan MO, Ali M. Swine Flu: Knowledge, Attitude, and Practices Survey of Medical and Dental Students of Karachi. Cureus, 2018 Jan 09; 10(1): e2048.
8. Nelson MI, Souza CK, Trovão NS, Diaz A, Mena I, Rovira A, Vincent AL, Torremorell M, Marthaler D, Culhane MR. Human-Origin Influenza A(H3N2) Reassortant Viruses in Swine, Southeast Mexico. Emerging Infect. Dis, 2019 Apr; 25(4): 691-700.
9. Masoudi S, PloenD, Hildt E.Is there an Association between the H1N1 Influenza Pandemic Vaccination and the Manifestation of Narcolepsy? J Vaccines Vaccin, 2015; 6(3): 1000280.
10. Webster RG, Bean WJ, Gorman OT, Chambers TM, Kawaoka Y) Evolution and ecology of influenza A viruses. Microbiol Rev., 1992; 56: 152-179.
11. Chen JM, Sun YX, Chen JW, Liu S, Yu JM, et al. Panorama phylogenetic diversity and distribution of type A influenza viruses based on their six internal gene sequences. Virol J, 2009; 6: 137.
12. Sebastian MR, Lodha R, Kabra SK Swine origin influenza (swine flu). Indian J Pediatr, 2009; 76: 833-841.
13. Shaik IK, Narain JP. Pandemic Disease Swine Flu: H1N1 Virus Clinical and Prevention Aspects RRJPPS | Volume 4 | Issue 1 | January -March, 2015.
14. Jang H, Boltz DA, Webster RG, Smeyne RJ. Viral parkinsonism. Biochim Biophys Acta, 2009; 1792: 714–21.
15. Maurizi CP. Why was the 1918 influenza pandemic so lethal. The possible role of a neurovirulent neuraminidase? Med Hypotheses, 1985; 16: 1–5.
16. Ravenholt RT, Foege WH. 1918 influenza, encephalitis lethargica, parkinsonism. Lancet, 1982; 2: 860–4.
17. Maricich SM, Neul JL, Lotze TE, Cazacu AC, Uyeki TM, Demmler GJ, et al. Neurologic complications associated with influenza A in children during the 2003-2004 influenza season in Houston, Texas. Pediatrics, 2004; 114: e626–33.
18. Studahl M. Influenza virus and CNS manifestations. J Clin Virol, 2003; 28: 225–32.
19. Stephen M. Maricich, Jeffrey L. Neul, Timothy E. Lotze, Andreea C. Cazacu, Timothy M. Uyeki, Gail J. Demmler, Gary D. Clark. Neurologic complications associated with Influenza A in children during the 2003–2004 Influenza Season in Houston, Texas. Paediatrics, 2004; 114(5).
20. Drago L, Attia MW, DePiero A, Bean C. Influenza A-associated meningoencephalitis. Pediatr Emerg Care, 2005; 21: 437–9.
21. Thompson W, Shay D, Weintraub E, et al. Mortality associated with influenza and respiratory syncytial virus in the United States. JAMA, 2003; 289: 179–186.
22. Hasegawa S, Matsushige T, Inoue H, Shirabe K, Fukano R, et al. (2011) Serum and cerebrospinal fluid cytokine profile of patients with 2009 pandemic H1N1 influenza virus-associated encephalopathy. Cytokine, 54: 167-72.
23. Ito Y, Ichiyama T, Kimura H, Shibata M, Ishiwada N, et al. (1999) Detection of influenza virus RNA by

reverse transcription-PCR and proinflammatory cytokines in influenza-virus-associated encephalopathy. J Med Virol, 58: 420-425.
24. Masson A. Post-influenza acute psychosis in an old man. Ann Med Psychol (Paris), 1957; 115: 490–4.
25. Rubin GJ, Amlôt R, Page L, Wessely S. Public perceptions, anxiety, and behaviour change in relation to the swine flu outbreak: Cross-sectional telephone survey. BMJ, 2009; 339: b2651.
26. German-Diaz M, Pavo-Garcia R, Diaz-Diaz J, Giangaspro-Corradi E, Negreira-Cepeda S. Adolescent with neuropsychiatric symptoms associated with novel influenza a (H1N1) virus infection. Pediatr Infect Dis J., 2010; 29: 570–1.
27. Joiner TE, Pfaff JJ, Acres JG, Johnson F. Birth month and suicidal and depressive symptoms in Australians born in the Southern vs. the Northern hemisphere. Psychiatry Res, 2002; 112: 89–92.
28. Maurizi CP. Influenza and mania: A possible connection with the locus ceruleus. South Med J, 1985; 78: 207–9.
29. Machón RA, Mednick SA, Huttunen MO. Adult major affective disorder after prenatal exposure to an influenza epidemic. Arch Gen Psychiatry, 1997; 54: 322–8.
30. McCall S, Henry JM, Reid AH, Taubenberger JK. Influenza RNA not detected in archival brain tissues from acute encephalitis lethargica cases or in postencephalitic Parkinson cases. J Neuropathol Exp Neurol, 2001; 60: 696–704.
31. Hansen MK, Nguyen KT, Goehler LE, Gaykema RP, Fleshner M, Maier SF, et al. Effects of vagotomy on lipopolysaccharide-induced brain interleukin-1beta protein in rats. Auton Neurosci, 2000; 85: 119–26.
32. Jang H, Boltz D, Sturm-Ramirez K, Shepherd KR, Jiao Y, Webster R, et al. Highly pathogenic H5N1 influenza virus can enter the central nervous system and induce neuroinflammation and neurodegeneration. Proc Natl Acad Sci U S A, 2009; 106: 14063–8.
33. Menninger KA. Psychoses associated with influenza, I: General data: Statistical analysis. JAMA, 1919; 72: 235–41. Menninger KA. Psychoses associated with influenza, I: General data: Statistical analysis. JAMA, 1919; 72: 235–41.
34. Battle YL, Martin BC, Dorfman JH, Miller LS. Seasonality and infectious disease in schizophrenia: The birth hypothesis revisited. J Psychiatr Res, 1999; 33: 501–9.
35. Bagalkote H, Pang D, Jones PB. Maternal influenza and schizophrenia in the offspring. Int J Ment Health, 2001; 29: 3–21.
36. Brown AS, Begg MD, Gravenstein S, Schaefer CA, Wyatt RJ, Bresnahan M, et al. Serologic evidence of prenatal influenza in the etiology of schizophrenia. Arch Gen Psychiatry, 2004; 61: 774–80.
37. Taller AM, Asher DM, Pomeroy KL, Eldadah BA, Godec MS, Falkai PG, et al. Search for viral nucleic acid sequences in brain tissues of patients with schizophrenia using nested polymerase chain reaction. Arch Gen Psychiatry, 1996; 53: 32–40.
38. Brown AS, Derkits EJ. Prenatal infection and schizophrenia: A review of epidemiologic and translational studies. Am J Psychiatry, 2010; 167: 261–80.
39. Nabeshima A, Ikematsu H, Yamaga S, Nakagawa M, Umezaki T, Hara H, et al. A case of an elderly patient with dementia and gait disturbance associated with influenza. Kansenshogaku Zasshi., 1997; 71: 944–8.
40. Eriksen W, Sundet JM, Tambs K. Register data suggest lower intelligence in men born the year after flu pandemic. Ann Neurol, 2009; 66: 284–9.
41. National Institute for Clinical Excellence. Guidance on the use of zanamivir, olsetamivir and amantadine for the treatment of influenza: Technology appraisal guidance. 4th ed. Washington, DC; National Institute for Clinical Excellence, 2010.
42. Turner D, Wailoo A, Nicholson K, Cooper N, Sutton A, Abrams K. Systematic review and economic decision modeling for the prevention and treatment of influenza A and B. Health Technol Assess, 2003; 7: iii–iv. xi–xiii, 1–170.
43. Toovey S, Rayner C, Prinssen E, Chu T, Donner B, Thakrar B, et al. Assessment of neuropsychiatric adverse events in influenza patients treated with oseltamivir: a comprehensive review. Drug Saf, 2008; 31: 1097–1114.
44. Maxwell SR. Tamiflu and neuropsychiatric disturbance in adolescents. BMJ, 2007; 334: 1232–1233.
45. Fuyuno I. Tamiflu side effects come under scrutiny. Nature, 2007; 446: 358–359. doi: 10.1038/446358a.
46. US Food and Drug Administration. The FDA safety information and adverse event reporting program.12th ed. New York: US Food and Drug Administration; 2011. Safety alerts for drugs, biologist, medical devices, and dietary supplements.
47. Toovey S, Rayner C, Prinssen E, Chu T, Donner B, Thakrar B, et al. Assessment of neuropsychiatric adverse events in influenza patients treated with oseltamivir: A comprehensive review. Drug Saf, 2008; 31: 1097–114.
48. Kohen I. Oseltamivir-induced delirium in a geriatric patient. Int J Geriatr Psychiatry, 2007; 22: 935–6.
49. Kitching A, Roche A, Balasegaram S, Heathcock R, Maguire H. Oseltamivir adherence and side effects among children in three London schools affected by influenza A (H1N1), May 2009 - an internet-based cross-sectional survey. Euro Surveill, 2009; 14: 19287.
50. Smith JR, Sacks S. Incidence of neuropsychiatric adverse events in influenza patients treated with oseltamivir or no antiviral treatment. Int J Clin Pract, 2009; 63: 596–605.
51. Yoshino T, Nisijima K, Shioda K, Yui K, Kato S. Oseltamivir (Tamiflu) increases dopamine levels in

the rat medial prefrontal cortex. Neurosci Lett, 2008; 438: 67–9.
52. Izumi Y, Tokuda K, O'Dell K, Zorumski C, Narahashi T. Neuroexcitatory actions of Tamiflu and its carboxylate metabolite. Neurosci Lett, 2007; 426: 54–58.
53. Satoh K, Nonaka R, Ogata A, Nakae D, Uhehara S. Effects of oseltamivir phosphate (Tamiflu) and its metabolite (GS4071) on monoamine neurotransmission in the rat brain. Biol Pharm Bull, 2007; 30: 1816–1818.
54. Christian LM, Franco A, Iams J, Sheridan J, Glaser R. Depressive symptoms predict exaggerated inflammatory responses to an in vivo immune challenge among pregnant women. Brain Behav Immun, 2010; 24: 49–53.
55. Henry CJ, Huang Y, Wynne AM, Godbout JP. Peripheral lipopolysaccharide (LPS) challenge promotes microglial hyperactivity in aged mice that is associated with exaggerated induction of both pro-inflammatory IL-1beta and anti-inflammatory IL-10 cytokines. Brain Behav Immun, 2009; 23: 309–317.
56. To KK, Hung IF, Li IW, et al. Delayed clearance of viral load and marked cytokine activation in severe cases of pandemic H1N1 2009 influenza virus infection. Clin Infec Dis, 2010; 50: 850–859.
57. Ito Y, Ichiyama T, Kimura H, et al. Detection of influenza virus RNA by reverse transcription-PCR and proinflammatory cytokines in influenza-virus associated encephalopathy. J Med Virol, 1999; 58: 420–425.
58. Ichiyama T, Morishima T, Kajimoto M, et al. Matrix metalloproteinase-9 and tissue inhibitors of metalloproteinase 1 in influenza-associated encephalopathy. Pediatr Infect Dis J, 2007; 26: 542–544.
59. Blum A, Simsolo C. Acute unilateral sensorineural hearing loss due to H1N1 infection. Isr Med Assoc J., 2010; 12: 450.
60. Pandemic influenza: A priority for the neurological community. Lancet Neurol, 2009; 8: 869.
61. Landaverde JM, Danovaro-Holliday MC, Trumbo SP, Pacis-Tirso CL, Ruiz-Matus C. Guillain-Barré syndrome in children aged <15 years in Latin America and the Caribbean: Baseline ratesin the context of the influenza A (H1N1) pandemic. J Infect Dis, 2010; 201: 746–50.