Swine flu (H1N1) infection among patients with neurologic disorders

A review of published evidence

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ABSTRACT

لقد انتشر وباء أنفلونزا الخنازير في عام 2009م، وبالرغم من اختفاء أصداء هذا المرض فإن هناك الكثير مما يجب علينا تعلمه ومعرفته عن هذا المرض. لقد قمنا في هذا المقال بمراجعة المظاهر السريرية لهذا المرض ومدى تأثيره على الجهاز العصبي المركزي، حيث كانت الاضطرابات العصبية متخفية وتنطوي تحت الحالات الصحية الأخرى، بالإضافة إلى المشاكل العصبية الناتجة عن أخذ لقاحات فيروس هذا المرض. وأهم ما يجب التركيز عليه في هذا الوباء هو كون هذا المرض متوسط الدرجة ولكن بمعدل انتشار عالي، وهذا قد يترتب عليه عواقب وخيمة قد تضر بالأشخاص المصابين بالأمراض والاضطرابات المتخفية والتي تشمل الأمراض العصبية.

Although the 2009 Swine flu (H1N1) pandemic has apparently been abolished, there are still lessons to be learnt. We reviewed the clinical and pathological manifestations of CNS involvement of influenza A virus infection. Neurologic disorders were most commonly seen as underlying medical conditions in swine flu, and neurological complications of the H1N1 vaccination. The major point with regard to the H1N1 pandemic is a mild disease with high contagiosity, which can have severe outcomes in those with underlying diseases including neurological ones.

Neurosciences 2011; Vol. 16 (3): 213-216

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The world encountered the swine flu, H1N1, pandemic in 2009.[1] The unique features of this pandemic, including increased incidence of disease among the youth and middle aged, higher contagiousness, high fatality rate, the role of morbid obesity as a risk factor for increased hospital admission and mortality rates, and considerable amount of adverse events among pregnant women, differentiate H1N1 from the seasonal flu.[2] Some reports showed the absence of association with chronic diseases,[3] but more recent literature showed that most of the patients hospitalized or who died due to H1N1 infection had a history of co-morbid illnesses.[4] It is crucial to specify the high risk groups predisposed to long hospital stay, intensive care unit (ICU) admissions, or mortality. As available resources are limited to deal with such a pandemic, prediction of the underlying medical conditions that make patients more susceptible to complications from severe influenza provides us with invaluable information for establishing global, regional, and national action plans. According to the published reports, chronic respiratory disorders, especially asthma, rank first in the list of co-morbid illnesses that have been associated with swine flu hospitalizations and deaths.[5] Although neurologic disorders have been described among co-morbid illnesses associated with swine flu complications, lack of organized information does not lead us to appropriate evidence based decisions or policy making. Meanwhile, reports concerning the clinic-pathological aspects of neurological manifestations of swine flu and the susceptibility of particular neurological disorders to swine flu are scarce. Herein, we review the association of concurrent neurologic disorders with swine flu severity and provide some guidance for neurologists.

Clinical and pathological manifestations of CNS involvement of influenza A virus infection. Just 2 months after the initiation of the 2009 H1N1 pandemic, the first report of neurological complications associated with H1N1 was published.[6] Central nervous system involvement has been reported in influenza pandemics

as early as 1385.[7] The spectrum of acute neurological manifestations of an influenza infection ranges from febrile seizures to an encephalopathic state, presenting with mental and behavioral changes. Influenza infection has been speculated as a precedential event in diseases such as Reye's syndrome, Guillain-Barré syndrome (GBS), Kleine-Levine syndrome, and post-encephalitic Parkinsonism.[8] Long-term neurological sequels of influenza infection may be present. A decline in the intelligence coefficient of offspring born 6 to 9 months after an influenza pandemic has also been reported.[9] The exact mechanisms underlying neurovirulence properties of the influenza virus are not fully understood. Hypotheses that include the role of transient viremia and consequent immunopathologic reactions, by cytokines and chemokine induction, or direct CNS invasion have been proposed.[10,11] Such assumptions have been supported by research detecting significant levels of proinflammatory markers and influenza RNA in the CSF or brain tissue of those who developed post-influenza encephalitis and encephalopathy.[12-14]

Which portions of hospitalized patients with H1N1 have underlying medical conditions? Severe acute respiratory illness (SARI) and swine flu affect both healthy individuals and those with underlying co-morbid illnesses. As shown in **Figure 1**, the percentage of patients with an underlying disease varies from 33.3-68% of total cases, according to different studies.[15-18] Interestingly, the percentage of patients with underlying disease has increased in successive reports. One reason might be the evolution of surveillance systems in conjunction with better recording and reporting of patients diagnosed with swine flu. More importantly, the case fatality rate is much higher among patients with preexisting conditions. In a study by Valliant and colleagues[19] on the worldwide mortality of swine flu, 90% of these cases had at least one co-morbid illness.
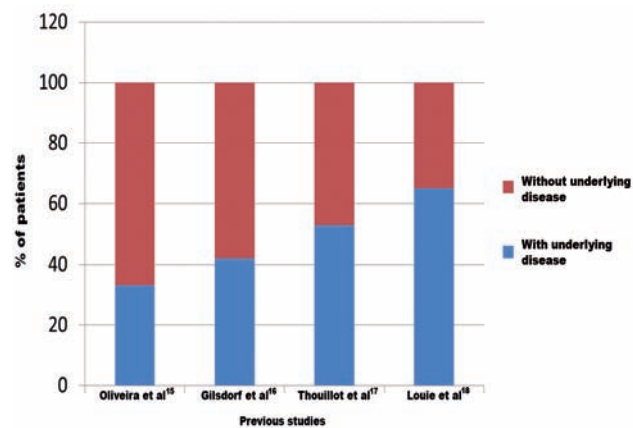

Figure 1 - Proportion of patients affected with H1N1 influenza that have underlying medical illnesses.

Which neurologic disorders were most commonly seen as underlying medical conditions in swine flu? Patients with neurological disorders were among the highest ranking groups susceptible to developing swine flu complications. For instance, in a report from Peru by Gómez and colleagues,[20] neurologic disorders ranked fourth after metabolic, cardiac, and respiratory diseases among co-morbidities and/or risk conditions in pandemic H1N1 influenza cases with fatal outcomes. In another report from Ireland,[21] chronic neurological disorders ranked second following asthma among risk groups as a percentage of the total Irish population. Furthermore, in this study, patients with chronic neurologic disorders had the longest hospitalizations in comparison with other high-risk groups. It should be mentioned that some patients had multiple co-morbid illnesses, including a single neurologic disorder or a combination of multiple neurologic disorders. Multiple medical conditions were additional risk factors in patients with H1N1 influenza.[22] The most important neurologic disorders, which have been reported as pre-existing conditions in an H1N1 infection were: cerebral palsy, seizure disorders, developmental delay, mental retardation, muscular dystrophies, stroke, quadriplegia, Parkinson's disease, and myasthenia gravis.[23-25] Most cases of reported H1N1 patients with neurologic disorders were less than 18 years-old. Considering the age factor, both genetic and metabolic diseases were more common in children, seizures in young and middle-aged adults, and dementias in geriatric patients.[23-25] Several studies have shown that children with neurologic disorders, especially those who have disabling conditions such as cerebral palsy, had more complications, hospitalizations, ICU admissions, and higher mortality, in comparison with adult patients.[26,27]

Neurological complications of the H1N1 vaccination. Immunization of an entire population against H1N1 does not seem to be affordable, particularly in developing countries. Khazeni et al[28] has shown that immunization of an entire population is not mandatory for reducing the pandemic's duration. Several cost-effectiveness studies have been conducted with regards to the immunization of particular groups. Beigi et al[29] has shown the cost-effectiveness of influenza vaccination during pregnancy in both seasonal influenza epidemics and occasional pandemics. However, studies that evaluated the cost-effectiveness of immunization against swine flu in patients with neurological disorders are limited. Therefore, immunization of patients with neurological disorders as well as mental and physical disabilities can be recommended as Class IV evidence-based medicine or Good Clinical Practice (GCP).

The neurologic complications of influenza vaccinations have always been a matter of debate and concern.[30] Although different studies have reported

a series of neurologic complications associated with seasonal influenza vaccination,[31] there are few reports regarding neurologic complications of the H1N1 influenza vaccination, such as GBS, thus far.[32] This is in contrast to the swine flu vaccinations in 1976, which were strongly associated with the development of certain neurologic disorders such as GBS.[33] In addition, until now, the H1N1 influenza vaccine has been reported to be safe in different age groups as well as in patients with chronic underlying medical conditions.[34] Interestingly, acute disseminated encephalomyelitis, which can also have a post-viral nature, has not been reported with immunization against swine flu. Accordingly, we have not found any confirmed reports of problems in patients with multiple sclerosis, myasthenia gravis, cerebral palsy, seizure, and cerebrovascular disorders after vaccination with swine flu.

It can be concluded that neurologic disorders are among the major co-morbid illnesses that predispose patients to develop severe H1N1 influenza, particularly among young age, and children. It seems the most susceptible groups of patients with neurologic disorders to develop complications of H1N1 influenza are children with neurodevelopmental conditions and disabilities, particularly cerebral palsy. This high-risk population needs special attention as a considerable percentage of them might be at risk due to social and family neglect. Education, vaccination, and treatment of H1N1 influenza in this group of patients can prevent detrimental consequences including prolonged hospitalization, ICU admission, and death.[35]

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Describe statistical methods with enough detail to enable a knowledgeable reader with access to the original data to verify the reported results. When possible, quantify findings and present them with appropriate indicators of measurement error or uncertainty (such as confidence intervals). Avoid relying solely on statistical hypothesis testing, such as the use of *P* values, which fails to convey important information about effect size. References for the design of the study and statistical methods should be to standard works when possible (with pages stated). Define statistical terms, abbreviations, and most symbols. Specify the computer software used.