Review

H1N1 infection and embolic events
A multifaceted disease

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ABSTRACT
H1N1 infection which affects a large number of people globally, is mainly regarded as a disease that affects the lung parenchyma. H1N1 infection is a multifaceted disease that beyond affecting the lung parenchyma, it affects the pulmonary vasculature as well. Even beyond this, it affects the vasculature in other parts of the body (either arteries or veins), and can cause other embolic events not strictly falling in the "usual" thrombotic category. This review, the first on this subject, tries to bring to focus what is known in the literature up to now, raise the awareness about the complications of the H1N1 disease, and alert the various medical specialties involved in the treatment of this multifaceted disease. These embolic events occur mostly (but not only) during pandemics.
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INTRODUCTION

H1N1 a worldwide spread disease affects millions of people each year. Pandemic influenza A/H1N1 virus seems to have originated from a blend of the North American swine virus with the NA and M segments of a European swine virus. In Mid-Spring of 2009, an outbreak of H1N1 influenza A virus infection was detected in Mexico, with subsequent cases reported in many other nations[1]. The majority of cases of pandemic H1N1 virus were relatively mild and without complications. The most common clinical manifestations include fever, headache, cough, myalgias, sore throat, fatigue and chills. Diarrhea and vomiting have also been common, both of which are unusual features of seasonal influenza. Influenza viruses can be transmitted through coughing and sneezing via large-particle droplets. In addition to secretions of the respiratory system, certain other bodily fluids like diarrheal stool should also be considered as potentially infectious. Gastrointestinal manifestations appeared to be more common with pandemic H1N1 influenza A[2]. During the pandemics, respiratory failure, rapidly progressive pneumonia, acute respiratory distress syndrome, embolic episodes including pulmonary embolism (PE) were reported in some cases[3-8]. H1N1 infection is mainly regarded as a disease that affects the lung parenchyma. However this is not

the only case. H1N1 infection is a multifaceted disease that beyond affecting the lung parenchyma, it seems that affects the pulmonary vasculature as well. Even beyond this, it affects the vasculature in other parts of the body (either arteries or veins), and can cause other embolic events not strictly falling in the thrombotic category. The purpose of this review is to show that H1N1 infection is a systematic disease, and raise awareness on the risks that this systematic involvement poses. This is the first review published to-date on this topic.

REVIEW OF THE LITERATURE

A search on Pubmed (and other resources) using "H1N1 infection" and "embolic events" or "pulmonary embolism" as the main search criteria returned 12 articles to support the hypothesis that H1N1 virus is a cause of embolic events. Does H1N1 infection induce an embolism? It seems that it does. Are these episodes life threatening? Yes, some of them are. Do we need to take action? Absolutely! And yes, we should concern. We need to be aware of them in order to diagnose and treat them, or even better to prevent them. Bibliography lists articles related to H1N1 infection with various embolic events. These are pulmonary artery blockage events, vascular and cardiovascular events or "other" embolic events which show a remarkable involvement of the H1N1 virus. Those events which occur mostly (but only) during pandemics, will be listed below. All references available on major sources (like Pubmed) were included in this review, if they supported the issue under review. At the time of this manuscript submission this list is considered complete (September 2016).

Intravascular coagulation was known to complicate influenza virus infections since quite a long time[9,10]. Venous thromboembolism (VTE) has been reported to complicate bacterial infections as well[11-13]. The pathophysiology of thrombosis is based on the presence of three factors: Venous stasis endothelial injury, and hypercoagulability. Damage to vascular walls prevents endothelium from inhibiting coagulation and initiating local fibrinolysis. As Venous Thromboembolism (VTE) has many factors, detailed analysis should be performed in an effort to determine the underlying cause. Additionally to coagulation cascade activation, inflammatory response plays a role in the formation of thrombus via production of microparticles (MPs) that carry cell-specific molecules—proteins such as galectins[14]. Stimulation of monocytes, especially by galectin-1, leads to cell activation and tissue factor expression which triggers the coagulation pathway. Furthermore, oxygen free radicals that are produced during inflammation are known to induce thrombosis in microvessels via activation of platelet aggregation[15]. Infectious agents, including viruses, bacteria and parasites, may initiate this process. An in vitro study reported that endothelial and monocytes cells that were incubated with influenza were able to activate coagulation via endothelial dysfunction and elevated tissue factor levels[15,16].

In a 2009 article by Agarwal et al[3], it was reported that people with a severe case of the pandemic H1N1 flu are at elevated risk of pulmonary embolism. Contrast-enhanced CT scans showed pulmonary emboli in 5 of 14 subjects admitted to intensive care at a major university hospital during the spring wave of the pandemic. In contrast, none of 52 subjects with less severe illness (most treated as outpatients) had emboli. Such pulmonary artery blockages are rarely seen in association with seasonal flu, suggesting that physicians should keep a close watch for them. They also suggested that subjects who are severely ill with H1N1 are also at risk for developing pulmonary embolism, which should be carefully sought for on contrast-enhanced CT scans. As extensive disease was defined the involvement three lung zones, at least. It was seen in 93% of their intensive care group (subjects who were intubated), compared with 9.6% of those less severely affected, a difference that was significant at $P<0.001$. None of their second group (subjects not needing intubation) had more than 20% overall lung involvement on initial radiographs[3]. In the 2009 pandemic of H1N1, the CDC reported on the first ten seriously ill subjects with severe illness and acute hypoxemic respiratory failure associated with A/H1N1 infection, because they noticed that half of the subjects had a pulmonary embolism[17]. It was recommended to use DVT prophylaxis. Pregnant women were a particularly vulnerable group of subjects. Pulmonary embolism in a few pregnant women with H1N1 infection was reported by Oboho et al[18], who recommend annual influenza vaccination.

In an article by Avnon et al[4] it was reported that during a four-month period from September to December 2009 out of 20 subjects that they cared for, with confirmed pandemic influenza H1N1 by real-time reverse transcriptase-polymerase chain reaction test (rRT-PCR), thrombotic events were identified in five (25%) of the critically ill subjects. These were stroke, acute anterior S-T elevation, and deep vein thrombosis of the leg or the subclavian arteries. The arterial thrombotic events were unusual and surprising in their young aged subjects. They recommended that subjects with severe influenza A/H1N1 pneumonitis and respiratory failure be administered DVT prophylaxis in particular if there are additional risk factors

for thromboembolic events (TVE). It was pointed out that subjects with severe influenza A/H1N1 pneumonitis and respiratory failure should be administered DVT prophylaxis in particular if there are additional risk factors for thromboembolic events.

Mauad et al[19] reported that in autopsies of 21 subjects with confirmed A/H1N1 infection four of them (19%) were confirmed with pulmonary embolism. One of the subjects had thrombotic angiopathy. This is in contrast to a Spanish report on 382 subjects with ARDS unrelated to A/H1N1 pneumonitis, when they found three subjects with pulmonary embolism among the subjects in whom diffuse alveolar damage was not revealed at the post-mortem examination, although clinically and physiologically they were diagnosed as ARDS[20]. This stresses out the fact that subjects with severe A/H1N1 infection experienced a high frequency of thromboembolic events more so than subjects with usual causes of ARDS and sepsis, and that arterial thrombosis in those subjects is of particular concern.

Harms et al[5] performed autopsies on eight subjects with fatal novel H1N1 infection and compared them with eight controls (non influenza related subjects) and reported that five out of eight subjects in the influenza group had peripheral pulmonary vascular thrombosis, while three out of eight in the non influenza group did. Thrombosis was prominent in the H1N1 group.

Pregnant women infected by influenza A (H1N1) 2009 virus have more severe disease and higher mortality but the pathogenesis for this is not clear. Chan et al[21] showed in mice that higher mortality, higher pulmonary viral load, more severe pneumonitis, lower peripheral blood T-lymphocytes and antibody responses, higher levels of proinflammatory chemokines and cytokines, and worse fetal development occurred in pregnant mice than non-pregnant controls infected by either wild type (clinical isolate) or mouse-adapted mutant virus with D222G substitution in hemagglutinin. These disease-associated changes and the lower respiratory tract involvement were worse in pregnant mice challenged by mutant virus. They concluded that the adverse effect of this pandemic virus on fetal and maternal outcome is mainly related to the severe pulmonary disease and the indirect effect of inflammatory cytokines spillover into the systemic circulation.

In another article Ona et al[22] reported influenza A (H1N1) virus as a cause of fulminant myocarditis. They reported a fatal case of fulminant myocarditis presenting as an acute ST-segment elevation myocardial infarction and ventricular tachyarrhythmia associated with influenza A/H1N1 in a previously healthy young pregnant woman. Fetal compromise was noted on the monitor, and the subject underwent an emergency cesarean section. Unfortunately, she subsequently expired. Autopsy was performed and confirmed severe myocarditis. This case of a lethal, yet rare complication of H1N1 infection emphasizes the importance of increased awareness among health care professionals to provide pregnant women with early vaccination and prompt treatment.

In a rare case, H1N1 virus was responsible for peripheral symmetrical gangrene in a woman without any predisposing factors. The cellular degeneration inflammatory mediators that were released during viral replication could be the contributing factor for its causation[23].

Bunce et al[24] reported that during the summer and fall of 2009, a significant number of thrombotic events were observed in subjects infected with the pandemic H1N1 influenza A virus. In a retrospective chart review of 119 individuals admitted to the hospital with H1N1 virus infection, seven subjects (5.9%) were found to have experienced thrombotic vascular events, four of which were venous and three of which were arterial in origin. All subjects who experienced thrombotic events had received DVT prophylaxis with subcutaneous unfractionated heparin. Two other subjects with H1N1 infection had presumed pulmonary emboli, although neither of these cases were confirmed, and they were not included in their analysis.

Beurtheret et al[25] reported that during 2009 the pandemic influenza A/H1N1 affected France and many subjects developed acute respiratory distress syndrome that was associated with influenza A/H1N1 virus. They used extracorporeal membrane oxygenation (ECMO) as therapeutic solution. All not confirmed cases of influenza A / H1N1 were excluded from the study. Eight subjects (66.6%) suffered significant hemorrhage requiring transfusion of more than two packed red cells. In two subjects (16.6%), there was a thrombosis of the inferior vena cava and one of them experienced pulmonary embolism. The observed rate for VTE was low, but nevertheless is another case of these episodes occurring with surprising frequency in H1N1 subjects.

Gökce et al[26] reported a sixteen-year-old female that developed deep vein thrombosis (DVT) while undergoing treatment for H1N1 pneumonia. This case was complicated by DVT in an adolescent subject with no detected risk factors other than immobilization. H1N1 infection in the presented case might have triggered the formation of thrombosis. The authors stress out that healthcare providers should be aware of the possibility of thrombosis in subjects with swine-origin influenza.

Van Wissen et al[8] in their study reported that influ-

enza infections have been associated with procoagulant changes. They state that whether influenza infections lead to an increased risk of pulmonary embolism remains to be established. They contacted their study as nested case control study in a large cohort of subjects with a clinical suspicion of having pulmonary embolism. Blood samples were collected to investigate the presence of influenza A and B by complement fixation assay (CFA). They compared case subjects, in whom pulmonary embolism was proven (n=102), to controls, in whom pulmonary embolism was excluded (n=395). Furthermore, they compared symptoms of influenza-like illness in both subject groups 2 weeks prior to inclusion in the study, using the influenza-like illness (ILI) score, which is based on a questionnaire. They calculated the risk of pulmonary embolism associated with influenza infection. Results showed that the percentage of subjects with influenza A was higher in the control group compared to the case group (4.3% versus 1.0%, respectively, odds ratio 0.22; 95% CI: 0.03-1.72). Influenza B was not detectable in any of the cases and was found in 3 of the 395 controls (0.8%). The ILI score was positive in 24% of the cases and 25% in the control persons (odds ratio 1.16, 95% CI: 0.67-2.01). They did not observe an association between the ILI score and proven influenza infection. They concluded that in this clinical study, influenza infection in general, was not associated with an increased risk of acute pulmonary embolism. The ILI score is non-specific in this clinical setting. H1N1 was not specifically evaluated, and this just one paper that does not support the hypothesis, and at the time of the publication of this paper the effect of specific subtypes on embolic events was not sufficiently evaluated. Although van Wissen et al[8] came to this result about the seasonal influenza virus, it seems from previous reports mentioned above that H1N1 is associated with acute pulmonary embolism. Embolic episodes are related to the specific subtypes and not the seasonal ones. Dülger et al[27] demonstrated the importance of considering pulmonary embolism as a diagnosis in 2009 pandemic influenza A (H1N1) virus infected persons who present with sudden onset of dyspnea, fever and chest pain.

There are anecdotal reports on the role of oseltamivir which is commonly used to treat H1N1 infection, on the development of thromboembolic events (oseltamivir is supposed to induce them), but no evidence for this was found on Pubmed or other resources.

Could influenza virus simulate pulmonary embolism if Computed Tomography Pulmonary Angiography (CTPA) is unavailable and perfusion scans are used to establish a PE diagnosis (ie in the case of bronchial obstruction or atelectasis)? Probably not if we thoroughly investigate the subject with ventilation scans as well[28,29]. In any case with the advent of CTPA misclassification is uncommon.

Other non thrombotic embolic events have been described making the role of H1N1 virus in the development of them enigmatic. Sabat et al[30] reported the case of a 22-year-old obese asthmatic woman with influenza A (H1N1)-associated acute respiratory distress syndrome who died from cerebral artery gas emboli with massive cerebral infarction, while she was treated with High-Frequency Oscillatory Ventilation in the absence of a right to left intracardiac shunt.

Kristufkova et al[31] who investigated fatal amniotic fluid embolism (AFE) cases in pregnant women in Slovakia from 2005-2010, found that five out of six subjects died during the 2009 H1N1 outbreak.

The table summarizes the studies referring to H1N1 infection and embolic events. Almost half of them are case reports, but the issue under review is an emerging one and you cannot dismiss any evidence that supports it.

Is there a role for vaccination? The answer is: Yes, there is. Influenza vaccination can reduce the risk of cardiovascular events in subjects with coronary heart disease, but its impact on the risk of venous thromboembolism (VTE) had not been studied. It was the aim of Zhu et al[32] to investigate whether influenza vaccination reduces the risk of VTE. They conducted a case-control study involving 1,454 adults enrolled in 11 French centers between 2003 and 2007. Subjects, had been vaccinated against influenza during the previous 12 months. After multivariate regression analysis, the odds ratios (OR) for VTE associated with vaccination were 0.74 (95% confidence interval [CI], 0.57-0.97) and 0.52 (95% CI, 0.32-0.85), respectively, for the whole population and for subjects aged 52 years or less. The protective effect of vaccination was similar for deep venous thrombosis (OR 0.9, 95% CI, 0.60-1.35) and pulmonary embolism (OR 0.71, 95% CI, 0.53-0.94) and for both provoked (OR 0.71, 95% CI, 0.53-0.97) and unprovoked VTE (OR 0.85, 95% CI, 0.59-1.23). They suggest that influenza vaccination is associated with a reduced risk of VTE. The role of vaccination in the prolepsis of embolic events has been praised in various studies, obviously by blocking the infection[18,22,32,33].

Vaccination is mandatory for pregnant women who are known to suffer severe disease[18,22]. Pregnant women are a high risk population for embolic events.

CONCLUSION

H1N1 infection is a serious global epidemic. It affects

TABLE 1. Studies supporting the hypothesis that H1N1 infection is a cause of various embolic events in humans.

Author	Number of patients studied	Number of patients with embolic events	Type of embolic events
Agarwal et al (2009)[3]	66	15	Pulmonary embolism
Avnon et al (2015)[4]	252	5	DVT of subclavian and jugular vein, DVT of leg, cerebral infarction
Bunce et al (2011)[24]	119	7	Pulmonary embolism, myocardial infarction, bilateral massive DVT, arterial thrombus of infrarenal aorta, thrombosis of right external Iliac vein and common femoral vein
Dülger et al* (2011)[27]	1	1	Pulmonary embolism
Gocke et al* (2012)[26]	1	1	Pulmonary embolism
Harms et al (2010)[5]	8	5	Peripheral Pulmonary Vascular Thrombosis
Kaulgud et al* (2013)[23]	1	1	Symmetric Peripheral Gangrene
Kristufkova et al* (2014)[31]	6	6	Amniotic fluid embolism
Ohrui et al* (2010)[7]	2	2	Pulmonary microthromboembolism
Ona et al* (2012)[22]	1	1	Myocardial infarction
Sebat et al* (2013)[30]	1	1	Cerebral gas embolism
Smeeth et al (2006)[13]	7278 (with DVT) 3755 (with PE)	**Risk=2.10% **Risk=2.11%	DVT Pulmonary embolism

* Case report, ** The authors report the risk (%)

people on all latitudes often with fatal results. Considering the vast lack of information on H1N1 and the prevalence of thromboembolic events, the importance of testing for pulmonary embolism or other embolic events at least subjects with severe respiratory failure and severe clinical presentation, needs to be stressed out. Rates of those events as mentioned above range from 20-50% of the population studied. At the moment the medical community is relatively unaware of this potential risk that may contribute to a fatal outcome in subjects with H1N1 infection. Surprisingly, this seems to be an underdiagnosed issue in H1N1 subjects with severe disease, and needs to be brought back from obscurity. Respiratory implications of H1N1 infection in terms of an affected lung parenchyma may not be the only cause of death. Involvement of pulmonary artery vessels is another important cause of disease severity and/or of a fatal outcome. Chest physicians focus on the involvement of lung parenchyma mainly in the H1N1 infection and not deal enough with the vascular involvement. H1N1 subjects are not investigated routinely for embolic events. It is not clear if the thrombi in pulmonary vasculature are developed locally or travel to the lungs from a distant body location. Although that it may be speculated that immobilization might be a factor for VTE, in none of the referenced articles immobilization is considered a risk factor. Every medical specialty involved in the treatment of this multifaceted disease, should do their best to either prevent, diagnose or treat what is now regarded as a complication of the H1N1 disease but in the future might evolve into a syndrome. Critically ill patients are those prone to experience those events. Physicians are encouraged to investigate H1N1 subjects further for embolic events, at least those with severe disease. Apart from vaccination, the prophylactic administration of low molecular weight heparin or unfractionated heparin in severely ill subjects (at least) is also encouraged, until pulmonary embolism or other embolic events ruled out[4,27], provided that the benefits of anticoagulation are weighed against the risks.

H1N1 seems to be an infection with many aspects not fully investigated or understood. The present review summarized all the studies published to this date. What is needed to further clarify this subject? We need prospective studies on the relationship of influenza A/H1N1 and embolic events.

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