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Research Article

Resurgence of Viral Activity of Pandemic Influenza a (H1N1) 2009: A Report from a Tertiary Care Institute in North India

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Abstract

Context: Although WHO officially declared the H1N1 influenza pandemic to be over in August 2010 but the virus continues to circulate as seasonal influenza with varied degree of activity in different parts of world. There was a sharp increase in virus activity in 2015 at several centers in India. We hereby by describe the clinical profile of patients admitted to the swine flu intensive care facility of the institute from January to June 2015.

Aim: To describe the clinical profile of patients admitted to the swine flu intensive care facility of the institute from January to June 2015.

Setting and Design: Retrospective observational study. All patients admitted with diagnosis of H1N1 influenza were included in the study.

Material and Methods: Epidemiological profile of all patients admitted with confirmed diagnosis of H1N1 influenza and their clinical details were recorded.

Results: Sixty eight patients (83%) had evidence of respiratory failure at admission. Twenty two (26.9%) of these had mild illness which resolved with antiviral therapy, oxygen supplementation and supportive management. Assisted ventilation was needed in 46 (56%) patients, of which 32 (39%) required Invasive Mechanical Ventilation (IMV) and 20 (24.4%) were managed with Non-Invasive Ventilation (NIV). Seven patients failed non-invasive ventilation and required endotracheal intubation and mechanical ventilation. Overall all-cause mortality was 28% however it was 65.6% in patients requiring mechanical ventilation.

Conclusion: H1N1 influenza carries high mortality in patient requiring hospitalization and assisted ventilation but timely institution of close monitoring and assisted ventilation can reduce mortality significantly.

Key Messages: The current study underscores and reiterates the fatal potential of H1N1 influenza. Looking at this persistence of viral activity in Indian subcontinent it is warranted to concentrate on education and preventive measures. The behavior of virus over last few years also calls for efforts from policy makers to frame guidelines and provision of vaccination for prevention and control of influenza.

Introduction

A new Swine-Origin Influenza Virus (S-OIV), A (H1N1), was identified in first quarter of 2009 in Mexico and the USA. Antigenic ally unrelated to human seasonal influenza viruses, this virus was result of reassortment of 4 distinct genetic elements, namely, swine, human, avian, and Eurasian swine genetic components [1]. As a result of its probable swine origin it was named as Swine-Origin Influenza Virus (S-OIV) which became responsible for first H1N1 pandemic of this century. This is the reason it is also referred to as pandemic influenza A (H1N1) 2009 virus (H1N1 2009 pdm).

Whenever there is major antigenic variation in the circulating influenza viruses predominantly in haemagglutinin (HA) component there is emergence of an influenza pandemic. In 20th century three pandemics were reported in 1918, 1957 and 1968 respectively. The antigenic property of the etiological virus was quite similar to the original 1918 A (H1N1) virus [2,3]. After 1998 there has been significant antigenic variation because of reassortment of these viruses with avian antigens and later when it combined with antigen with of swine origin there was emergence of this novel influenza virus to which there was no herd immunity and it resulted in reemergence of the pandemic [4]. Since April 2009, there was rapid human to human transmission and the virus spread across various countries which resulted in considerable morbidity and mortality. World Health Organization declared pandemic alert level to 6 on June 11, 2009 because of the potential of virus to affect children and young adults, spread rapidly and associated mortality and morbidity [5]. Although WHO officially declared the pandemic to be over in August 2010 but the virus continues to circulate as seasonal influenza with varied degree of activity in different parts of world.

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Table 1: Demographic profile and baseline clinical characteristics of patients.

Symptom	Total (n=82)	Survivors (n= 58)	Non survivors (n= 24)	P-value
Mean age	43.73±14.26	42.38±14.53	47.00±13.33	0.18
Duration of illness	7.36±5.23	7.62±5.73	6.75±3.80	0.49
Gender				
Male	41 (50)	29 (50)	12 (50)	1
Female	41 (50)	29 (50)	12 (50)	1
Presenting symptoms				
Sore throat	20 (24.4)	14 (24.1)	6 (25)	0.9
Dyspnoea	68 (82.9)	44 (75.9)	24 (100)	0.008
Fever	71 (86.6)	53 (64.6)	18 (75.0)	0.07
Cough	73 (89.0)	53 (91.3)	20 (83.3)	0.47
Vomiting	7 (8.5)	7 (12.0)	0	0.1
Hemoptysis	5 (6.1)	2 (3.4)	3 (12.5)	0.14
Myalgia	2 (2.4)	2 (3.4)	0	0.5
Diarrhoea	2 (2.4)	1 (1.7)	1 (4.1)	0.5
Chest pain	1 (1.2)	0	1 (4.1)	0.2
Rhinorrhoea	1 (1.2)	0	1 (4.1)	NS
Abdominal pain	1 (1.2)	1 (1.7)	0	0.5
Headache	1 (1.2)	1 (1.7)	0	0.5
Laboratory parameters				
Hematocrit				
Leucocyte count	9.58±5.81	7.92±3.64	13.36±7.88	<0.01
Platelets count (per mm^3)	210.50±118.67	230.82±130.02	161.37±64.37	0.02
Serum creatinine (mg/dL)	1.49±1.41	1.16±1.01	2.29±1.28	0.01
AST (U/L)	193.98±640.28	91.98±114.34	466.0±1189.5	0.02
ALT (U/L)	103.61±210.05	77.58±114.64	169.86±350.33	0.08
ALP	132.00±119.59	109.89±46.59	190.95±208.24	<0.01

Values are expressed as mean ± SD or numbers (%) unless specified.

In India 27,236 people were affected in 2009 and about 20000 laboratory confirmed cases were reported in 2010. The attributable mortality reported in 2009 and 2010 was 33.59 and 8.55% respectively [6]. There was a period of quiescence from 2011 to 2014 but in 2015 there was a resurgence of activity at several centers in India, Rajasthan, Gujarat and Uttar Pradesh being the most affected.

We hereby by describe the clinico-epidemiologic profile of patients admitted to the swine flu intensive care facility of the institute from January to June 2015.

Material and Methods

This was a retrospective observational study in which case records of all patients with confirmed diagnosis of H1N1 influenza admitted to the swine flu intensive care facility of the institute from January to June 2015 were evaluated. Epidemiological profile and clinical details were listed with special reference to severity of respiratory failure, hospital and ICU length of stay and overall case fatality.

The Acute Physiology and Chronic Health Evaluation (APACHE) II score was used to assess the severity of illness [7]. All patients requiring assisted ventilation and vasopressor support for circulatory failure were classified as "severe disease". Risk factors for severe disease and unfavorable outcome like, presence of chronic obstructive pulmonary disease, asthma, diffuse parenchymal lung disease, underlying cardiac illness, malignancy, chronic liver or renal diseases, diabetes mellitus, and presence of an immunocompromised state due to any reason were also enlisted.

Table 2: Comorbidities and complications among survivors and non survivors.

	Total (%)	Survivors (%)	Non survivors (%)	P-value
Co-morbidity				
DM	20 (24.3)	12 (14.6)	8 (9.7)	0.17
HTN	19 (23.1)	6 (7.3)	13 (15.8)	0.5
COPD	5 (6.1)	3 (3.7)	2 (2.4)	0.9
ILD	1 (1.2)	0	1 (1.2)	0.1
CKD	2 (2.4)	1 (1.2)	1 (1.2)	0.5
CAD	4 (4.8)	3 (3.7)	1 (1.2)	0.8
Hypothyroidism	7 (8.5)	7 (8.5)	0	0.07
Pregnancy	3 (7.3)	2 (4.8)	1 (2.4)	0.8
Complications				
Shock	30(36.5)	9(10.9)	21(25.6)	<0.01
MV	32 (39.0)	11 (13.4)	21(25.6)	<0.01
NIV	14 (17.0)	11 (13.4)	3 (3.7)	0.4
ARDS	28 (34.1)	9 (10.9)	19 (23.1)	<0.01
AKI	12 (14.6)	2 (2.4)	10 (12.1)	<0.01
DIC	4 (1.2)	1 (1.2)	3 (3.7)	0.03

Values are expressed as numbers (%): for pregnancy parenthesis represents percent per total females (41).
*DM: Diabetes Mellitus; HTN: Hypertension; COPD: Chronic Obstructive Pulmonary Disease; ILD: Interstitial Lung Disease; CKD: Chronic Kidney Disease; CAD: Coronary Artery Disease; MV: Mechanical Ventilation; NIV: Non-Invasive Ventilation; ARDS: Acute Respiratory Distress Syndrome; AKI: Acute Kidney Injury; DIC: Disseminated Intravascular Coagulation.

Diagnosis of H1N1 influenza was made by RT-PCR from nasopharyngeal swab specimens and respiratory secretions. RT-PCR was performed in the department of microbiology of our institute. Viral RNA was extracted from all samples by using the QI Aamp Viral RNA mini kit as per the manufacturer protocol. RNA was amplified by one step RT PCR kit (Agpath-IDTM, Ambion) on Real Time PCR platform (ABI 7500 standard, USA) by user's manual. Specific primer and probe sequences targeting pdm 2009 were taken from CDC.

Briefly, In 25μL reaction volume contained 12.5μL 2X buffer, 0.5μL of each primer and probe, 1.0μL of 25X enzyme mix (Taq DNA polymerase and reverse transcriptase), 5.0 μL of nuclease free water and 5.0μL of extracted RNA. The amplification was carried out 50^0C for 30 min., 95^0C for 10 min followed by 40 cycle of 95^0C for 15 sec. and 55^0C for 30 sec.

The study protocol was approved by the Institutional Ethics Committee.

Results

During the study period a total of 2893 samples were tested at

Table 3: Characteristic of patients with respiratory failure.

	Non ventilated (N=36)	NIV (N=20)		IMV (N=33)	P value
		NIV Success (N=13)	NIV Failure (N=7)		
Age	42.31±1.4	49.31±10.8	43.2±21.9	43.11±14.5	0.5
Total days of illness	8.05±6.8	6.38±3.37	6.57±2.37	7.00±3.5	0.6
Total admission days	6.47±4.3	10.23±5.5	12.57±8.3	14.24±10.2	0.018
CXR quadrants	1.42±1.4	2.92±1.1	3.57±1.1	3.39±1.1	0.2
APACHE	4.86±4.7	9.25±4.59	11.29±4.0	11.48±6.5	0.005
PF ratio	306.2±92.5	213.18±65.9	211.7±119.7	150.29±92.9	0.2
28 day mortality (no.)	0	3	4	11	

Values are expressed mean ± SD or numbers unless specified. P values represent the difference between NIV and IMV group. NIV: Non-Invasive Ventilation; IMV: Invasive Mechanical Ventilation.

our institute, of which 739 were tested positive for H1N1 2009 pdm. Out of these 82 patients required admission to the swine flu intensive care unit of our institute. Mean duration of illness before hospitalization was 14.6 days. Cough, fever and breathlessness were the most common presenting symptoms. Apart from fever and dyspnea, the baseline clinical characteristics were similar among survivors and non survivors. There was no significant difference between the age of survivors and non survivors. On multivariate logistic regression analysis presence of dyspnea at presentation was the only independent risk factor for mortality. Among the laboratory parameters total leukocyte counts, serum creatinine, AST and serum alkaline phosphatase values were significantly higher and platelet count was significantly lower among the non survivors (Table 1).

The prevalence of comorbidities was also similar among survivors and non survivors (Table 2).

Sixty eight patients (83%) had evidence of respiratory failure at admission. Twenty two (26.9%) of these had mild illness which resolved with antiviral therapy, oxygen supplementation and supportive management. Assisted ventilation was needed in 46 (56%) patients, of which 32 (39%) required invasive mechanical ventilation (IMV) and 20 (24.4%) were managed with Non-Invasive Ventilation (NIV). Seven patients failed non-invasive ventilation and required endotracheal intubation and mechanical ventilation. Mean APACHE II score in patients requiring mechanical ventilation was 11.35 ± 6.6 however it was 9.25 ± 4.59 in patients who were successfully managed with NIV. There was no significant difference between patient requiring NIV and IMV with respect to age, duration of illness before presentation, PaO_2/FiO_2 ratio, and degree of radiological involvement and total duration of hospital stay (Table 3). Among the patients requiring mechanical ventilation 18 (56.4%) were males and 14 (43.6%) were females. Eleven patients requiring mechanical ventilation survived and 21 patients succumbed to their illness. Overall all-cause mortality was 28% however it was 65.6% in patients requiring mechanical ventilation.

Circulatory failure (39%) was the most common non pulmonary organ failure followed by acute kidney injury (14.6%). Requirement of mechanical ventilation, presence of Acute Respiratory Distress Syndrome (ARDS), Acute Kidney Injury (AKI) and Disseminated Intravascular Coagulation (DIC) at time of hospitalization were the most important predictors of mortality.

Table 4: Representative studies published about H1N1 Influenza.

Study/Journal	Study duration	No.	Patients requiring AV	Mortality
Siddharth V et al. **Indian J community Med 2012**	May 2009 to Apr 2010	54	-	28 (51.8 %)
Mathur et al. **JAPI 2013**	2009 – 2010	221	-	80 (36.2 %)
Maheshwari et al. **JAPI 2015**	Aug 2009 to May 2014	94	57	53 (56.3 %)
Mehta et al. **JCDR 2013**	June 2009 to Dec 2011	88	14	6 (6.8%)
Biswas et al. **IJMR 2010**	July 5 to Aug 2010	129	NA	NA
Patel et al. **J Glob Infect Dis. 2013**	Aug 2009 to Feb 2010	63	17	14 (22.2 %)
Kartik et al. **J Glob Infect Dis. 2012**	Sept 2009 to Nov 2009	106	96	52 (49.0 %)
Kumar et al. **N Am J Med Sci. 2012**	Aug 2009 to Apr 2011	32	32	20 (62.5 %)
Anand et al. **J Anaesthesiol Clin Pharmacol 2012**	July 2009 to June 2010	54	19	40 (74.0 %)

AV: Assisted Ventilation.

Discussion

The activity of seasonal influenza peaks during the months of Augusto March in South Asian region [8]. Although WHO had declared the H1N1 influenza pandemic to be over in August 2010,the virus still in continues to circulate as seasonal influenza all over the world. After a quiescence of about 5 years the beginning of this year was punctuated by a sharp resurgence of seasonal influenza activity in India. According to reports, probably it was the worst season since the inception of pandemic with highest influenza related morbidity. About 30,000 cases were reported till the end of March 2015 [9]. In the current study we also encountered increase in number of hospitalizations related to H1N1 influenza at our institute. Mean

age affected was similar in comparison to previous years and also to reports from different parts of country this year. There was no significant difference in age of survivors and non survivors. Presence of dyspnea at the onset of illness was the only symptom which was predictor of severe disease and also was associated with significantly high mortality (Table 1). Similarly, presence requirement of assisted ventilation, presence of circulatory failure, acute kidney injury and acute respiratory distress syndrome were independent predictor of mortality (Table 2).

Case fatality of H1N1 influenza had been a subject of debate since the beginning of pandemic. Highly variable mortality has been reported from around the globe. In a recent systematic review mortality rates ranging from less than 1 to more than 10,000 deaths per 100,000 cases or infections have been reported. There was significant heterogeneity in the results with the higher estimates based on laboratory-confirmed cases compared with symptomatic cases or infections. Therefore the authors suggested that there should be consensus on case definitions for estimation of mortality [10]. In various case series [8,11-18] published form India the overall mortality has been reported ranging from 7% to 74%. In our study the overall mortality was 28% however we also found high mortality among the patients requiring mechanical ventilation (34%) which is comparable to various case series published from different parts of country (Table 4). Most of the studies published from India describe the patient cohort from initial couple of years of the pandemic as a result of which the mortality rates reported were quite high. However with increased awareness about the condition most of the centers across the globe were better prepared to deal with outbreak both in terms of personnel and intensive care units who are directly involved in management and containment of epidemic.

As compared to last outbreak when 47840 cases and 2744 deaths were reported during May 2009 to December 2010, there was sharp increase in number of cases in 2015 with more than 35000 people infected and 2335 deaths from 1 January to 21 April 2015 [19]. In our study we also observed that the severity of illness as characterized by APACHE scores was quite high and ARDS on few occasions was refractory to conventional ventilatory strategies. Rescue strategies like "prone position ventilation" was required in 17 patients. The mean APACHE score and mean ventilator days were significantly higher in the patients requiring mechanical ventilation. The exact reason for increasing severity of illness in this season remains elusive and is a matter of concern which was also raised by researchers from Massachusetts Institute of Technology, USA who hypothesized that the currently circulating H1N1strain has undergone some genetic mutations which are responsible for increasing severity and infectiousness of the illness but the same was refuted by officials from the National Institute of Virology [9]. In another study a D222G mutation in haemagglutinin gene [20] has been described in isolates which has been linked with severe disease [21]. But no large studies are available to describe its role in current outbreak. This however calls for systematic study of isolates from different centers during an outbreak for minor or major antigenic shifts in virus structure. Looking at this persistence of viral activity in Indian subcontinent it is warranted to concentrate on education and preventive measures. According to WHO/CDC annual influenza vaccination is supposed to be the most effective method for prevention of influenza infection, its associated complications and consequently mortality. The Advisory Committee on Immunization Practices (ACIP) recommends annual influenza vaccination for everyone above 6 months of age for the year 2015-2016. Unfortunately a vaccination policy for prevention for influenza and related morbidity and mortality has not been framed in India as of now. It seems likely that further outbreaks and crisis situations can be avoided if a vaccination campaigns are initiated at least in "at risk" groups.

Conclusion

The current study underscores and reiterates the fatal potential of H1N1 influenza. Contrary to the belief based on earlier reports we found that it affects patients of all age groups and more that 60% patients in our studies had one or more comorbidities at admission. It carries high mortality in patient requiring hospitalization and assisted ventilation but timely institution of close monitoring and assisted ventilation can reduce mortality significantly. India observed one of the worst outbreak of H1N1 influenza this year and has given enough stimulus to researchers to work out the reasons behind this severe resurgence of viral activity in different parts of India. It also call for efforts from policy makers to frame guidelines and provision of vaccination for prevention and control of influenza.

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