CLINICAL CHARACTERISTICS AND RADIOLOGICAL MANIFESTATIONS IN INFLUENZA A AND (H1N1) SWINE FLU INFECTION: OUR EXPERIENCE

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ABSTRACT

BACKGROUND

The study was carried out during July 2017 through October 2017 when there was a seasonal epidemic of influenza like illness (ILI) in Odisha.

MATERIALS AND METHODS

We collected data of 36 cases confirmed out of 152 suspected cases by reverse - transcriptase - polymerase chain assay of sampling of nasopharyngeal swab or pharyngeal secretions at Regional Medical Research Centre (ICMR), Bhubaneswar from clinical presentations of influenza illness.

RESULTS

Results of the 36 confirmed patients studied, 9 were influenza A positive H1N1neg and 27 influenza A & H1N1 (swine flu) positive. 22.2% of cases were below 19 yrs., whereas those above 60yrs in both groups were 33.3% and 25.9% respectively. In the H1N1 positive cases, diabetes mellitus and cardiovascular disease each constituted 18.5% amongst the comorbidities. All cases underwent chest radiography on admission. Bronchovascular prominence and bilateral consolidation were most frequently observed (37.1 & 33.3% respectively). HRCT performed in cases having normal chest X-ray revealed tree in bud and nodular pattern. Out of the total confirmed cases, 4 died (11.1%). Qualitative risk factors like renal failure, sepsis and ARDS were associated with mortality (p value< 0.05). Quantitative risk factors like low mean arterial pressure and raised serum creatinine were associated with mortality (p<0.001). Use of antiviral drug Oseltamivir initiated at a mean of 5.83 days was beneficial among the survivors.

CONCLUSION

During the seasonal epidemics, influenza-A both H1N1 negative and positive cases caused illness requiring hospitalisation. Severe illness with renal failure, sepsis, hypotension, ARDS had mortality outcome. Patients seem to benefit from early antiviral therapy.

KEYWORDS

Influenza A, H1N1 (Swine flu), renal failure, sepsis, ARDS, Oseltamivir.

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BACKGROUND

Influenza virus A, B and C belong to Orthomyxovirus group. Influenza A has raised alarming concern for public health worldwide. Following its emergence in March 2009, Influenza A (H1N1) virus spread rapidly throughout the world leading to the declaration of an influenza pandemic by WHO on 11th June 2009. It is estimated that around 201, 200 patients died from respiratory diseases caused by influenza A (H1N1) pdm09 (swine Flu) and an additional 83,300 patients died from cardiovascular disorders associated with same virus infection.[1] The world is now in post-pandemic period.

In India it causes local out breaks. During 2014, India reported 937 cases and 218 deaths. In 2015, 42592 cases and 2990 deaths and in 2016, 1647 cases and 257 deaths due to Influenza H1N1 (Swine Flu) were reported.[2]

Influenza virus may cause sporadic infection or seasonal epidemics in geographical pockets to pandemics, if novel strain with sufficiently transmissibility potential infects people who are immune naïve.[3] The virus can transmit from person to person efficiently, especially in crowded and closed environments. There is increasing evidence of perennial circulation in tropical countries due to warmer, more humid climates.

The burden of pneumonia is markedly higher in very young and elderly.[4] Humans infected with influenza present with asymptomatic or self-limited mild illness. However, some may become victim with severe pneumonia, acute respiratory distress syndrome, and sepsis.[5,6] Risk factors of

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virus associated pneumonia including malnutrition, air pollution, tuberculosis, co morbid immune compromised conditions, tobacco exposure may play some role.

In addition to the direct cell and tissue damage induced by the virus, accumulated studies suggest that over-activated immune response also contribute to the severe complications of influenza.[7,8]

Clinically it is sometimes difficult to differentiate viral and bacterial pneumonia at presentation. However some distinctive clinical, biochemical, pulmonary radiological features may be encountered in viral pneumonias. It is important to pay attention to pulmonary imaging findings that may serve as early indicators of the presence and impending severity of disease. This may have an impact in timely management of critical cases.

Early medical attention, especially antiviral therapy, is essential for reducing severe complications and mortality outcome.[9,10] Most studies of these pneumonias have been performed in hospital settings due to serious illness at presentations. We share our experience in Kalinga Institute of Medical Sciences (KIMS), Bhubaneswar, Odisha, India - a tertiary care hospital relating to their clinical and radiological characteristics.

Aims and Objectives

1. To study the clinical and radiological presentations of laboratory confirmed influenza A and H1N1 (Swine flu) pneumonia admitted cases.
2. To identify the factors associated with mortality of the confirmed influenza A and Swine flu pneumonia admitted cases.

MATERIALS AND METHODS

It was a retrospective study based on clinical and radiological characteristics of cases of Influenza A and Swine flu, confirmed by Reverse transcriptase Polymerase Chain Reaction (RT-PCR) method on nasopharyngeal swab or pharyngeal secretion collected from 152 suspected cases attending our institute.

All suspected cases reported during seasonal epidemic from July 2017 through October 2017 were admitted and all routine investigations were done. Nasopharyngeal or pharyngeal swabs were collected and sent in viral transport medium immediately to the diagnostic reference laboratory with standard questionnaires, including demographic, epidemiological and clinical information. The swab samples underwent Reverse transcriptase Polymerase Chain Reaction (RT-PCR) assay method at Regional Medical Research Centre (ICMR), Bhubaneswar that uses one-step qualitative PCR probe hydrolysis (Taqman) kit on ABI-7500 equipment which is endorsed by WHO approved CDC protocol.

The cases were defined based on the diagnosis of influenza which was provided within 12 hours after the receipt of the samples. The suspected case of influenza A(H1N1) in the current study was defined as:

As a person with acute febrile respiratory illness (fever equal to or more than 38 degree C) with onset (a) within 7 days of close contact with a person who is a confirmed case of influenza A(H1N1) 2009 virus infection or; (b) with in 7days of travel to areas where there are one or more confirmed cases or (c) resides in a community where there are one or more confirmed influenza A(H1N1) 2009 cases.[11]

Data obtained included day of hospitalisation, demographics, symptoms, laboratory and, pulmonary imaging data including Chest X ray, HRCT thorax if done, time of initiation of antiviral therapy, requirement of ventilation and outcome of ventilator therapy. Any associated comorbidities if present were documented.

Chest X-Ray Evaluation

Each lung was divided into 3 zones- upper, mid and lower zones. The presence of any of the following including interstitial shadows, nodular opacities or consolidation was recorded.

The Ethics Committee of the Institute approved the collection of clinical data from the subjects with influenza A infection.

Statistical Analysis

All the clinical data were tabulated and the p values were reported for a meaningful association. For comparing mortality and survival, the relevant categorical data were tested either using by chi-square test or Fisher's exact test. Independent t-test was used to compare the means of two groups when quantitative data followed the normal distribution. A p value of 0.05 was considered as statistically significant. All the analysis was carried out using statistical software STATA version 13.1.

RESULTS

All the patients were hospitalised either in ward or ICU based on their clinical condition. Of the 152 suspected cases, total 36 cases were confirmed to be positive for influenza A virus, out of which 9(25%) were influenza A positive H1N1 negative and rest 27(75%) were Influenza A and H1N1(Swine flu) positive. Among patients who were Influenza A positive H1N1 negative, 6 were male and 3 were female, compared to 15 males and 12 females seen in H1N1 positive cases respectively. 6 cases less than 19yrs (22.2%) were infected with H1N1.

Duration of illness was more than 7 days in 11(40.7%) H1N1 positive cases compared to 2(22.2%) of H1N1 negative cases. The duration of less than 7 days was observed in 16 (59.2%) in H1N1 positive cases and 7 (77.7%) H1N1 negative cases respectively. The clinical presentations in the both groups (Influenza A positive H1N1 negative and influenza A positive H1N1 positive) were cough, fever, shortness of breath, sore throat, diarrhoea, vomiting, sputum, nasal catarrh, altered sensorium. Among the symptomatics, shortness of breath, sore throat, nasal catarrh and vomiting were more common in H1N1 positive than negative cases ($p < 001$; 0.016, 0.156 respectively) (Table 1).

Clinical Feature	Influenza A POS, (n=9)	Influenza A, H1N1 POS (n=27)	P Value
Cough	7 (77.7%)	25(92.5%)	0.225
Fever	7 (77.7%)	24, (88.8%)	0.581
Shortness of Breath	0	24(88.8%)	<0.001*
Sore throat	0	12(44.4%)	0.016*
Diarrhoea	3(33.3%)	7 (25.9%)	0.686
Vomiting	0	7(25.9%)	0.156
Sputum	3(33.3%)	3(11.1%)	0.151
Nasal Catarrh	0	7(25.9%)	0.156

Table 1. Signs and Symptoms on Initial Evaluation

Pulmonary involvement in radiology was seen in symptomatics having cough (88.8%), fever (86%), shortness of breath (66.6%), sore throat (33.3%), diarrhoea (27.7%), vomiting (19.4%) respectively (Table 2).

Clinical Features	X-Ray Positive (n=36)
Cough	32 (88.8%)
Fever	31(86%)
Shortness of Breath	24(66.6%)
Sore Throat	12(33.3%)
Diarrhoea	10(27.7%)
Vomiting	7(19.4%)

Table 2. Clinical Feature Profile among all X-Ray Positive Cases

(Both Influenza A positive and Influenza A H1N1 positive)

Pulmonary radiological abnormalities noticed in both groups included normal study, bronchovascular prominence, unilateral consolidation, bilateral consolidation and interstitial pattern. HRCT thorax revealed tree- in- bud and nodular shadows in those cases where bronchial markings, normal radiological pattern were noticed. HRCT also revealed ground glass opacity, consolidation pattern in other group of cases where patchy consolidation and hypoxemia were noticed as a part of clinical evaluation.

The values of haematological, renal, electrolytes are shown in Table 3. Leucocytosis was seen in 4(44.4%) and 15(55%) case in H1N1 negative and H1N1 positive groups respectively. Renal failure was observed in more (8(29.6%)) cases in H1N1 Positive cases than in H1N1 Negative (2 (22.2%)) patients. Raised C- reactive protein was detected in 3 cases in H1N1 Positive cases and one case who was H1N1 negative.

Pattern of Illness			
Characteristics	**Influenza - A +VE & H1N1 -VE**	**Influenza- A & H1N1 +VE**	**P Value**
	(n-9)	**(n-27)**	
Age			
Up to 19 years	0	6(22.2%)	0.020*
20 to 40 years	4 (44.4%)	1 (3.7%)	
40-60	2(22.2%)	13(48.1%)	
>60	3(33.3%)	7(25.9%)	
Gender			
Male	6(66.6%)	15(55.5%)	0.705
Female	3(33.3%)	12(44.4%)	
Clinical Pattern			
Pulmonary	7(77.7%)	20(74%)	1.000
Extra-Pulmonary (diarrhoea, vomiting)	3(33.3%)	7(25.9%)	
Duration			
<7 days	7(77.7%)	16(59.2%)	0.438
>7 days	2(22.2%)	11(40.7%)	
Comorbid Illness			
COPD	Nil	3(11.1%)	0.558
Obesity	1(11.1%)	1(3.7%)	
Cardiovascular Disease	1(11.1%)	5(18.5%)	
Cerebrovascular	1(11.1%)	1(3.7%)	
Diabetes	2(22.2%)	5(18.5%)	
CKD	1(11.1%)	2(7.4%)	
HIV	1(11.1%)	Nil	
Lab. Evaluation			
Leucocytosis	4(44.4%)	15(55.5%)	1.000
Renal Failure	2(22.2%)	8(29.6%)	
Dyselectrolytemia	Nil	1(3.7%)	
Raised CRP	1(11.1%)	3(11.1%)	
Chest X-Ray Abnormalities			
Normal	3(33.3%)	4(14.8%)	0.402
Bronchial Markings Prominence	1(11.1%)	10(37%)	
Unilateral Consolidation	1(11.1%)	6(22.2%)	
Bilateral Consolidation	3(33.3%)	9(33.3%)	
Interstitial pattern	1(11.1%)	1(3.7%)	
HRCT Thorax Findings			
Tree in Bud	2(22.2%)	3(11.1%)	0.295
Nodular pattern	0	3(11.1%)	
Ground Glass Pattern	0	4(14.8%)	
Patchy Consolidation	0	3(11.1%)	
Respiratory Failure			
Non-invasive support	Nil	2(7.4%)	1.000
Mechanical Ventilation Support	3(33.3%)	6(22.2%)	
Outcome of Ventilator Support			
Survivor	2(22.2%)	3(11.1%)	1.000
Death	1(11.1%)	3(11.1%)	

Table 3. Association of Demographic, Clinical Characteristics and Co-Morbidities with Influenza and H1N1

Comorbid conditions seen in both groups were COPD, obesity, cardiovascular disease, cerebrovascular disease, diabetes mellitus, chronic kidney disease and HIV (Table 4).

Co-Morbidity	X- Ray Positive
COPD	3(8.3%)
Obesity	2(5.5%)
Cardio-Vascular Disease	6(16.6%)
Diabetes	7(19.4%)
CKD	3(8.3%)
HIV	1(2.7%)

Table 4. Co-Morbidities and X-Ray Association (N=36)

A total of 11 cases developed respiratory failure of which 8(29.6%) were H1N1 positive and 3(33.3%) were negative for H1N1. Of the 8 H1N1 positive patients developing respiratory failure, 2 were managed with non-invasive ventilation while 6 required invasive ventilation. Out of the 36 patients, 4 patients died out of which 3 were H1N1 positive and 1 was H1N1 negative (Table 3).

All the patients received a course of Oseltamivir as soon as confirmation of diagnosis was made.

Survival and mortality patterns in total 36 cases of both H1N1 positive and H1N1 negative were analysed in relation to qualitative characteristics including age, sex, duration of illness, renal failure, sepsis, ARDS, comorbid illness, raised CRP and pulmonary radiological involvement. It was observed that amongst them renal failure, sepsis, ARDS had higher mortality which was statistically significant ($p<0.05$). Pulmonary radiological involvement more than 3 zones was seen in all mortality cases ($p =0.006$) (Table 5, 6).

Risk Factor	Classification (36 no. s)	Survivors (32) n (%)	Mortality (4) N (%)	P Value
Age	>60 (10)	9 (90%)	1 (10%)	1.000
	<60 (26)	23 (88.4%)	3 (11.6%)	
Sex	Male (21)	19 (90.4%)	2 (9.6%)	
	Female (15)	13 (86.6%)	2 (13.4%)	1.000
Duration of Illness	≥7 days (13)	10 (76.9%)	3 (23.1%)	0.124
	<7 days (23)	22 (95.6%)	1 (4.4%)	
Renal Failure	Present (10)	6 (60%)	4 (40%)	0.004*
	Absent (26)	26 (100%)	0	
Sepsis	Present (4)	1 (25.0%)	3 (75.0%)	0.002*
	Absent (32)	31 (96.9%)	1 (3.1%)	
ARDS	Present (10)	6 (60.0%)	4 (40.0%)	0.004*
	Absent (26)	26 (100%)	0	
Comorbid Illness	Present (24)	21 (87.5%)	3 (12.5%)	1.000
	Absent (12)	11 (91.6%)	1 (8.6%)	
Raised CRP	Present (4)	2 (50%)	2 (50%)	
	Absent (32)	30 (93.75%)	2 (6.25%)	0.053
Pulmonary radiological involvement more than 3 zones	Present (11)	7 (63.64%)	4 (36.4%)	0.006*

Table 5. Association between Different Qualitative Characteristics and Mortality

*-Statistically Significant with P value <0.05.

Association between Risk Factor & Mortality (36 cases) t-test			
Risk Factors	Mean (SD)		P value
	Survival (32)	Mortality (4)	
Age(years)	46.67 (21.31)	59.5 (12.66)	0.250
BP(MAP)	98.09 (7.61)	68.5 (18.65)	<0.001*
Day of initiation of Therapy	5.83 (3.33)	8.50 (3.11)	0.138
PaO2/FiO2	170.50 (22.01)	173 (25.02)	0.8338
WBC Count (Neutrophilic Leucocytosis)	13789.59 (6842.71)	14216.60 (2001.31)	0.928
Serum CREATININE	1.2993 (1.1349)	2.925 (0.499)	<0.001*
Pulmonary consolidation	4.63 (1.03)	5.50 (0.58)	0.110

Table 6. Association between Different Quantitative Characteristics and Mortality

*-Statistically Significant with P value <0.05.

DISCUSSION

We report 36 cases detected (9 cases of influenza A Positive, H1N1 Negative and 27 cases of influenza A Positive, H1N1 Positive) among 152 suspected cases by RT-PCR method at Regional Medical Research Centre, Bhubaneswar who presented to the hospital during the reported epidemic between July and October 2017. In patients with co-morbidities presenting with extra-pulmonary symptoms, abnormalities in chest x-ray were detected. Hence heightened awareness is needed to suspect swine flu on clinical grounds. Higher attack rates were reported among children, young adults compared to adults older than 60 years of age, this can be presumably due to exposure in persons older than 60yrs to antigenically related influenza virus in earlier life, resulting in the development of cross – protective antibodies.[12,13]

The pulmonary clinical features of cough, fever and expectoration were same in both groups but shortness of breath, sore throat and vomiting were seen more commonly in H1N1 Positive cases. Studies by Wang C et al describe similar clinical features of all hospitalised cases reported during seasonal and pandemics of H1N1 Influenza.[14]

Patients in our study had presence of underlying medical illness including COPD, obesity, cardiovascular disease, cerebrovascular disease, diabetes mellitus, chronic kidney disease and HIV out of which diabetes and cardiovascular disease were more common in H1N1 Positive cases (18.5%). This was lower when compared to published studies that depict around 44 to 84% of adults with seasonal influenza had underlying medical illness.[15,16,17]

In our study, a significant proportion of cases had findings of bronchopneumonia or pneumonia suggested by bilateral infiltrate on chest radiograph. It is difficult to differentiate viral or bacterial etiology of pneumonia from radiograph. L ABBO et al reported findings of bilateral infiltrate in patients with primary influenza viral pneumonia.[18] Some of the patients progressed from influenza symptoms to pneumonia, manifested by bilateral consolidation findings on chest radiograph consistent with the acute respiratory distress syndrome requiring mechanical ventilation. Thus in contrast to seasonal influenza A which runs a self- limited course, most of the serious illness are caused by H1N1 (swine flu)virus.

All the four cases that died needed ICU admission because of disease severity. Renal failure, sepsis, ARDS and hypotension were associated with mortality which was statistically significant. Similar studies of elevated creatinine in critical H1N1 cases were reported by Dominguez Cherit et al, Cao B et al, Perez-Padilla et al.[19,20,21]

Al the cases were administered Oseltamivir as soon as the diagnosis was confirmed in a dose of 75mg twice daily for 5 to 7 days depending upon the severity of the illness. Bacterial co-infection in those cases showing leucocytosis, pulmonary infiltrates were administered beta-lactam antibiotics at the time of hospitalisation. Recommendation[22] suggests that treatment with Oseltamivir therapy should be initiated in hospitalised patients even if such therapy is initiated more than 48 hours after the onset of symptoms and also approved its use in children. In our series among the survivors the mean (SD) value of day of initiation of therapy was 5.83(3.33) where that in the mortality group was 8.50(3.11). However the difference was not statistically significant (p=0.138).

Thus based on knowledge about past pandemics the (H1N1) 2009 virus is expected to circulate as a seasonal virus for some years to come and cause concern to some extent. Vigilance on the part of national health authorities remains important when the behaviour of H1N1 virus as a seasonal virus cannot be reliably predicted.[23] On 26th September2011 WHO has adopted a new nomenclature as Influenza A (H1N1) pdm09[24] for this virus.

CONCLUSION

In conclusion we found patients tested for Influenza A H1N1 negative had milder clinical course than those who were H1N1 positive. H1N1 illness can cause illness in young. Extensive consolidation as pulmonary radiological involvement mirrors the severity of the disease. There was mortality of 11.1% among 36 cases hospitalised with clinical picture of influenza with multiple complications like renal failure, ARDS, hypotension in elderly. Early administration of Oseltamivir is beneficial. High index of suspicion in seasonal epidemic period can lead to early detection.

Limitations of the Study

Small sample size of the mortality group led to a lack of infallible conclusion.

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