

Clinical characteristics and outcome of H1N1 (2009) pneumonia with special reference to radiological features in a tertiary care hospital in northern Karnataka

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Abstract: *Background:* In late March 2009, an outbreak of respiratory illness, later proved to be caused by swine origin influenza A (H1N1) virus (S-OIV) was identified in Mexico. Thereafter many countries worldwide have reported the incidence of this pneumonia. The present study was undertaken to evaluate the clinical characteristics and radiological features of positive cases of confirmed Influenza A H1N1 (2009) infection in a tertiary care hospital in northern part of Karnataka. *Material and Methods:* A retrospective analysis of medical charts, laboratory investigations and radiographs of 57 positive cases of Influenza A H1N1 (2009) infection was done. Throat swab of all these patients were confirmed by real time RT-PCR assay (reverse transcriptase polymerase chain reaction method). *Results:* A total of 57 cases were infected with influenza A H1N1 (2009) virus. They belonged to 20 to 40 years of age, with the mean age being 35. Acute onset cough, fever and breathlessness were the most common clinical presentation. Some of them had chest pain, sore throat, rhinitis, hemoptysis and vomiting. Twenty patients had co-morbid conditions like type 2 diabetes mellitus, IHD and one of them was a case of carcinoma breast on chemotherapy. Features of leucopenia, leucocytosis, thrombocytopenia, raised liver function parameters and raised blood serum creatinine were the major laboratory features. Radiologically, almost all of the patients had confluent ground glass appearance on chest radiographs, with bilateral distribution of the patchy infiltrations in multiple lung zones. A typical consolidation was conspicuous by its absence. Pleural effusion was present in 14% of the cases. A total of 35 patients required mechanical ventilation and 26 of them succumbed to death. Hypoxemia and thrombocytopenia were the major risk factors for the mortality with H1N1 pneumonia. It was also observed that involvement of four or more lung zones and bilateral peripheral opacities was associated with higher mortality in these patients. Raised liver function test parameters and raised serum creatinine levels were the indicators for development of MODS. Mortality on mechanical ventilator for these patients was very high ($p < 0.0008$). *Conclusions:* The present study revealed the serious nature of H1N1 pneumonia with high mortality due to ARDS and MODS in patients requiring mechanical ventilation. This emphasizes the need for early institution of the antiviral therapy and close monitoring in these patients.

Keywords: H1N1 pneumonia, radiological features, clinical features, mortality, correlates.

Introduction

In 2009, the world experienced a novel Influenza A H1N1 pandemic which stressed critical care delivery systems with an onslaught of patient with severe, life threatening respiratory failure [1]. This new strain of Influenza A H1N1 virus was identified first in Mexico. The pandemic A(H1N1) virus originated from the triple-reassortment swine influenza (H1) virus circulating in North American pigs [2-3]. Worldwide 14,286 deaths were reported by January 18, 2010 [4]. India too was a part of this pandemic and confirmed its first case in May 2009 [5]. Following this a large number of positive cases were diagnosed to have H1N1

pneumonia throughout the country. Very few studies have been reported from India which has studied the clinical characteristics of these patients. Hence the present study was undertaken to evaluate the clinical characteristics and radiological features of positive cases of confirmed Influenza A H1N1 (2009) infection in a tertiary care hospital in northern parts of Karnataka.

Material and Methods

A retrospective review of medical charts, laboratory investigations and radiographs of 57 positive cases of Influenza A H1N1 (2009) infection was done. Throat swab of all these

patients were sent to NIMHANS, Bangalore and National Viral Institute, Pune for confirmation by real time RT- PCR assay (reverse transcriptase polymerase chain reaction method) in accordance with the protocol from the US centers of disease control and prevention as recommended by WHO [6].

A total of 57 confirmed cases of Influenza A H1N1 were reported in the tertiary care hospital over a period of 2 years. The patients were diagnosed to have pneumonia if the chest radiograph showed abnormalities which were consistent with pneumonia. This included consolidation, ground glass appearance, infiltrations which were either patchy or confluent or reticular pattern on chest radiographs. All these patients required intensive care monitoring, 35 patients required mechanical ventilation due to severe hypoxemia (ARDS presentation) and 26 of them succumbed to death.

Results

Demographic profile: A total of 57 cases were infected with influenza A H1N1 (2009) virus were included in the study. Mean age group of the patients was 35 and majority of them belonged to 20 to 40 years of age. Both men and women were almost equally affected (Table 1). All the patients were admitted with complaints of acute onset cough, fever and breathlessness. Some of them had chest pain, sore throat and rhinitis. Very few of them had hemoptysis and vomiting. Twenty patients had co-morbid conditions. Nine had type 2 diabetes mellitus, ten of them had IHD and one of them was a case of carcinoma breast on chemotherapy.

Characteristics	No. (%)
Age (years)	
<10	3 (5.26)
10-20	3 (5.26)
20-30	17 (29.82)
30-40	16 (28.07)
40-50	13 (22.80)
50-60	5 (8.77)
Sex	
Male	32 (56.14)
female	25 (43.85)

Symptoms	
Fever	57 (100)
Cough	57 (100)
Dyspnoea	57 (100)
Chest pain	29 (50.87)
Sore throat	20 (35.08)
Rhinitis	10 (17.54)
Hemoptysis	4 (7.01)
Vomiting	12 (21.05)
Co-morbidities	20 (35.08)
Diabetes mellitus	9 (15.78)
IHD	10 (17.54)
Ca breast	1 (5.26)
Admitted in nursing homes and referred	8 (14.03)
Possible source of infection	
Travel to endemic area	15 (26.31)
Contacted infection from family members	3 (5.26)
Residing in urban/semiurban area	35 (61.40)

Laboratory data: A total of 29 patients (50.8 %) showed features of leucopenia or leucocytosis. Nineteen patients (33.33%) had thrombocytopenia. Few of the patients (15.78%) showed raised serum creatinine and significant percent of them had raised liver enzymes. Hypoxia at room air or with supplemental oxygen administration again was one of the significant finding especially among the patients who expired. A total of 32 patients (56.14%) had severe hypoxemia (pao2 < 60mmHg) at room air and all of these patients did not show any improvement in oxygenation status even after oxygen supplementation. These patients required mechanical ventilation for the management of severe hypoxemia. None of the female patients in our study group were pregnant (Table 2).

Characteristics	No. (%)
Hemoglobin (g/dl) (mean)	11.45
Normal(11- 16)	30 (52.63)
Mild anemia(9.5-10.9)	14 (24.56)
Moderate anemia(8-9.4)	6 (10.52)
Serious anemia(6.5-8)	4 (7.01)
Life threatening anemia(<6.5)	3 (5.26)

Characteristics	No. (%)
Leucocytosis (>11000/cmm)	15 (26.32)
Leucopenia (<4000/cmm)	14 (24.56)
Thrombocytopenia (< 1,65,000/cmm)	19 (33.33)
Thrombocytosis (> 350,000/cmm)	8 (14.03)
Sr. Creatinine (>1.5mg%)	18 (15.78)
Elevated total bilirubin(> 1.2 mg/dl)	10 (17.54)
AST (>83.62 U/L)	30 (52.63)
ALT (>95 U/L)	30 (52.63)
ALP (>140 U/L)	14 (24.56)
pO2 (< 60mm Hg)	32 (56.14)

Radiological features: Radiological pattern of all the patients were analyzed in detail for various abnormalities (Table 3). Chest radiographs of all the patients (100%) showed confluent ground glass opacities. Most of them (66%) showed confluent opacities while few (25%) showed patchy opacities. Almost 93% of patients had both central and peripheral distribution and all of them had multi zonal involvement. Characteristic consolidation was absent in all the patients. All the patients had multiple zones of involvement and not a single patient had single lobar distribution of the disease (Fig. 1-4). Majority of the patients had bilateral involvement with 75% having bilateral involvement as their initial presentation and the rest had unilateral involvement. Eight patients (14%) presented with pleural effusion.

Table-3: Radiological findings of H1N1 pneumonia	
Characteristics	No. of patients (%)
Opacity	
Ground glass	57 (100)
Consolidation	none
Patchy	14 (24.56)
Nodular	none
Confluent	38 (66.66)
Distribution	
Central	4 (7.12)
Peripheral	none
Both	53 (92.98)
No. of zones	
Single	none
Multiple	57 (100)
No. of sides involved	
Unilateral	6 (10.5)
Bilateral	51 (89.5)
Pleural effusion	8 (14.03)

Fig-1: Chest radiograph showing bilateral dense consolidation



Fig-2: Chest radiograph showing bilateral ground glass appearance



Fig-3: Chest radiograph showing ARDS pattern due to H1N1 pneumonia



Fig-4: Chest radiograph showing localized right upper lobe pneumonia



Outcome: A total of 26 patients died on mechanical ventilation due to ARDS and MODS. On multivariate analysis it was observed that hypoxemia, $pao_2 < 60\text{mmHg}$ and serum creatinine $> 1.5 \text{ mg/dl}$ and hospital stay < 5 days were independent risk factors for mortality from H1N1

pneumonia ($p < 0.05$) (Table 4). It was also observed that starting the patients on mechanical ventilation had higher risk of deaths ($p < 0.01$). None of the other factors were associated with high risk of deaths in these patients.

Table-4: Risk factors for mortality for H1N1 pneumonia (logistic regression analysis)

Characteristics	Expired (n=26)	Improved (n=31)	Odds Ratio	95% CI	P value
Age groups: ≤ 30 years	12	10	0.69	0.26-1.87	0.47
Gender: Female	11	14	1.06	0.41-2.74	0.89
Thrombocytopenia	15	4	0.22	0.06-0.75	0.01
Presence of any coexisting condition	10	10	0.83	0.3-2.32	0.73
Mechanical Ventilation	26	9	0.29	0.11-0.72	0.008
Leucocytosis	4	11	2.30	0.65-8.11	0.19
Leucopenia	7	6	0.71	0.21-2.40	0.59
Complications on MV	3	1	0.27	0.27-2.85	0.2
PO2 ($< 60\text{mm Hg}$)	52.41 \pm 13.44	74.74 \pm 17.23	-	-	0.013
Sr. Creatinine ($> 1.5\text{mg/dl}$)	1.94 \pm 1.58	0.86 \pm 0.28	-	-	0.045
Hospital stay in days: ≤ 5 days	4.75 \pm 2.66	8.82 \pm 4.96	-	-	0.051

Discussion

This study reports the clinical characteristics of the confirmed cases of 2009 novel influenza A H1N1 who required hospitalization and intensive care unit, from August 2009 to December 2010. Most of the patients in this case series are middle aged. Age group of population involved with H1N1 pneumonia worldwide is variable in different studies done in other parts of the world [7-10]. This varied presentation may be due to the ubiquitous involvement of the H1N1 virus in any age group person without any predisposing factor. Regarding the source of infection of contracting H1N1 disease, a total of 16(26.3%) had travel history to endemic area for H1N1 infection. It was also noted from the history that majority of patients (61.4%) were residing in the urban or semi-urban areas. They might have contracted H1N1 infection due to the dense population in these areas. Only three patients had history of contracting the infection from other family members.

Both men and women were equally involved due to H1N1 infection. The clinical presentation remained similar to those from other countries worldwide [11-12] with fever, dry cough and

dyspnoea being the major symptoms. Other symptoms that were present included chest pain, sore throat and rhinitis. Two patients each had hemoptysis and vomiting respectively. Presence of co-morbid conditions is always not associated with increased risk of H1N1 pneumonia.

In the present study, more than one-third patients (35.08%) had co-morbidities like IHD and DM. One patient had carcinoma of breast, operated and was on chemotherapy. One study [13] has found that individuals with co-morbid conditions like bronchial asthma, COPD, diabetes mellitus, cardiac disease were more susceptible for H1N1 viral infections. Since the sample size of this case series is small it is difficult to correlate the association of co-morbidities with the influenza infection in the present study. Clinically, tachycardia and tachypnoea were observed in all the patients. More than 90% of the patients were hypoxemic and nearly half of the cases had significant hypoxemia and it was observed to be one of the independent risk factor for mortality in those patients with H1N1 pneumonia.

The presence of leucocytosis or leucopenia were the common laboratory findings in patient with H1N1 pneumonia (40.88%). Other studies have also observed similar findings in H1N1 pneumonias. Thrombocytopenia was also observed in significant number of cases, which has also been reported in other studies [5], and it is one of the independent risk factor for mortality due to H1N1 pneumonia. Nearly half of the patients had liver dysfunction at the time of initial presentation and 15% had raised creatinine level in the blood. This suggests that H1N1 pneumonia patients may rapidly progress to multi-organ dysfunction syndrome (MODS) due to the release of inflammatory mediators in the blood which may contribute to overall higher mortality. The raised liver function parameters have also been found in other Indian study done by Chudasama et al [14].

The radiological presentations in H1N1 pneumonia were varied ranging from ground glass appearance to confluent or patchy opacities, reticular pattern, multi-zonal involvement and bilateral in distribution. Pleural effusion was observed in 14% of the cases. These findings are consistent with those observed by other authors [15]. Aviram et al [15] studied in detail the radiological presentation in H1N1 pneumonia and they observed radiological opacity to be of ground glass in nature in majority of patients (69%), predominantly central location and less frequently observed in peripheral location. Consolidation was also frequent in occurrence which was either patchy in distribution or presented as rounded nodular opacities. In one third of patients air bronchogram could be detected and mid lung zones were most frequently involved sites compared to lower lung zones. A total of 8% of the patients had pleural effusion with one third of them having bilateral effusions. They also observed that involvement of four or more lung zones and bilateral peripheral opacities was associated with higher mortality in these patients. Ajlan et al [16] also observed ground-glass opacities and consolidations in most of the H1N1 pneumonia patients. However, hazy areas of increased opacity without obscuration of the underlying vessels (ground-glass opacities) were by far the most common finding in their study, being more commonly bilateral than unilateral. They also noted that none of patients showed a reticular or nodular pattern on the initial or follow-up radiographs. Another observation

was that the progression of radiographic abnormalities was mostly in the form of developing multifocal areas of consolidation on follow-up.

Rapidly progressive respiratory failure is relatively common and about 10% to 30% of hospitalized patients have required ICU admission [14]. Intermittent mandatory ventilation, with a lung-protective ventilation strategy, is recommended as the initial approach for managing patients with pandemic A (H1N1) infection complicated by ARDS. Non invasive positive pressure ventilation is generally not recommended for patients with the novel influenza infection complicated by pneumonia and ARDS. NPPV temporarily improves oxygenation and reduces the work of breathing, but does not necessarily alter the course of the disease. The WHO interim guidelines on prevention and control of acute respiratory diseases in health care have included NPPV among those aerosol generating procedures in which there is possibly increased risk of respiratory pathogen transmission [17]. Almost 61% of the patients in the present study required invasive mechanical ventilation for the management of severe hypoxemic status. Non invasive ventilation was tried in some of the cases but it was not successful. Similar trend has been observed in several other studies [14]. The mortality rate was as high as 72% among those cases who were mechanically ventilated. The higher mortality rates in the present study indicate the serious nature of the disease or they rapidly progressed to ARDS and MODS. Similar higher mortality rate with H1N1 pneumonia has been observed by Chudasama et al [14] and Perez-Padilla et al [18] of 81.6% and 58% respectively. Lung damage in these patients is most likely due to primary effect of infection with influenza virus or possibly due to the viremia, as was reported in association with H5N1 infection which is a aggressive variety of influenza [13]. Coinfection with other respiratory viruses would also explain the increase pathogenicity in these patients [16]. It has also observed that cardiac dysfunction is a common complication associated with hospitalized pandemic A H1N1 [19]. It may also contribute to the higher mortality in these patients with the

preexisting cardiac diseases. Early recognition of this syndrome could facilitate initiation of both timely and appropriate therapy.

Chudasama et al [14] in their study has noted several risk factors that were independently associated with increased mortality with H1N1 pneumonia. These included hospital stay more than five days with H1N1 pneumonia delay in starting antiviral drugs, presence of coexisting conditions and pregnancy. Obesity, treatment in nursing homes and higher APACHE II score has also been reported to be important risk factors for higher mortality with H1N1 pneumonia [13]. Obesity may contribute to severe disease and may be more common in identified racial/ethnic groups. Second, ethnic communities may have had an epidemic spread of novel A (H1N1). Third, Hispanics or Pacific Islanders may have a genetic predisposition for a more severe manifestation of A (H1N1) infection. Finally, race/ethnicity, lack of medical insurance, and younger age may be related to less access to care, such that socioeconomic factors, rather than genetic predisposition, may be responsible for severe disease due to novel A H1N1 infection [13]. In the present study, after logistic regression analysis, it was observed that thrombocytopenia, hypoxemia, serum creatinine > 1.5 mg/dl and initiation of mechanical ventilation were associated independently with higher mortality with H1N1 pneumonia.

Current CDC guidelines for pandemic and seasonal influenza recommend the use of either Oseltamivir or Zanamivir for hospitalized patients with suspected or confirmed influenza and for outpatients who are at risk for complications [20]. Early initiation of antiviral therapy (within 48 hrs) has been observed to be beneficial and is associated with fewer complications [21]. Antiviral therapy for influenza is hampered by the early peaking of the viral load, which leaves a

narrow window of opportunity for antiviral treatment [22]. In both seasonal and pandemic A H1N1 influenza A infection, the viral loads peaked at around 1 to 2 days post symptom onset in natural infections of healthy adults with or without oseltamivir treatment. Although oseltamivir was shown to hasten recovery and reduce viral load, its long-term effectiveness for pandemic A H1N1 remains uncertain. Despite the apparent efficacy of oseltamivir in mild cases, its efficacy in stopping further disease progression of late cases remains uncertain [23]. A study has reported that patients admitted to ICU or died were less likely to have received such therapy within 48 hrs after onset of symptoms [24]. Chudasama et al [14] has reported mortality up to 90% in severe disease patients even after complete course of Oseltamivir therapy, possibly because of delayed referral and initiation of antiviral drugs. Though all the patients received Oseltamivir therapy on first day of admission, the effect could not be assessed as most of the cases were referred and had variable duration, from onset of symptoms to presentation to our centre. This delay in the presentation also contributed to the higher mortality in our study.

In conclusion, our study revealed the potential nature of influenza A H1N1 pneumonia progressing to ARDS and MODS resulting in increased mortality, and since patient's presentation to the tertiary care hospital following symptoms onset was varied, the apparent efficacy of oseltamivir in stopping further disease progression especially in late cases remained uncertain. Extensive involvement of both lungs, as expressed by the presence of multi-zonal involvement and bilateral peripheral opacities on chest radiograph was associated with adverse prognosis.

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