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ATYPICAL FORM OF PANDEMIC A (H1N1) INFLUENZA

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Abstract

Introduction: The clinical picture of the pandemic influenza A (H1N1) ranges from a self-limiting non-febrile infection to a rapidly progressive pneumonia. The aim is to highlight the existence and the prevalence of atypical forms of pandemic influenza and its clinical presentation.

Patients and Method: This observational prospective study was conducted in the Infectious Diseases Hospital of the UHC "Mother Theresa", Tirana over the period May 2009 - March 2010. Laboratory confirmation of 2009 (H1N1) virus infection was performed within 2 days after admission. Atypical forms of pandemic influenza (AFPI) were regarded patients presented with no classic influenza syndrome.

Results: 52 out of 363 of cases with pandemic flu admitted at infectious diseases hospital were AFPI. The prevalence of AFPI was 14.3%, 95% CI 11.1-18.2. 24 (46.2%) were women and 28 (53.8%) were men. The mean age of patients was 46 years (SD± 13). No significant differences in gender and age resulted between patients with AFPI, p= 0.09. Thirty three (63.5%) cases had a diagnosis of Pneumonia, 11 (21.2%) ARI with fever, 5 (9.6%) Septic syndrome and 3 (5.8%) Encephalopathy, $\chi 2=43.6$, $p < 0.01$. The level of oxygen saturation during the ARI resulted in 80-95% in 15 cases; 70-80% in the 6 and under 70% in 8 cases, $\chi 2=4.6$ p = 0.09. There is a significant difference between patients with atypical and typical influenza in regard with regard to clinical and biochemical features of illness.

Discussion: Clinical suspicion of atypical presentations of influenza should involve pregnant women, patients with immune-suppression that were associated with laboratory findings.

Key words: hypoxemia, pandemic influenza, pneumonia, symptoms.

Introduction

The clinical spectrum of presentation of pandemic influenza ranges from a self-limiting non-febrile upper respiratory tract infection to a rapidly progressive lower respiratory tract disease, resulting in intensive care unit admission in 25% of patients and in death in 7% (1). Although underlying co-morbidities are common, severe illness has been reported from the 2009 pandemic (H1N1) virus infection among young healthy people, including pregnant women (2) and children (3).

The vast majority of patients presented at infectious diseases hospital with clinical features of influenza which includes sudden onset of fever (>38°C), cough and sore throat, and rhinorrhea in the absence of other diagnosis (4). However, a proportion of admissions were observed in patients who presented with uncommon symptoms and were regarded as atypical form of pandemic influenza (AFPI). The atypical influenza pattern is not specific, being present in situations as pneumonia, acute respiratory infections, septic syndrome and encephalopathy (5, 6). Pneumonia is the most frequent pattern in AFPI.

There were atypical forms of influenza with a wide variety of clinical presentation, from upper respiratory illness without fever to fulminant pneumonia (7, 8, 9, 10).

The accuracy of diagnosis varies substantially, depending on whether the case occurs sporadically or during a recognized outbreak, when a typical presentation of influenza-like illness is likely to represent 2009 H1N1 virus infection. However, the wide clinical spectrum of 2009 H1N1 virus infection and its features that overlap those of

other common infections have sometimes led to the misdiagnosis of certain respiratory viruses (Para-influenza virus and respiratory syncytial virus (11, 12).

There was typically rapid progression of occult influenza within four to five days of the onset of illness. Patients presented with clinical signs of tachypnea, hypoxemia, hypotension and/or diarrhoea and high levels of lactate dehydrogenase, creatine-kinase, and creatinine. Lymphopenia was common, usually appearing on the second day and lasting until the seventh day (13, 14, 15, 16). The radiologic diagnosis is widely used in the emergency department thus becoming a standard tool because it provides a non-invasive reliable examination for early diagnosis and the consequent start of antiviral treatment in hospitalized patients, reducing disease severity and mortality (17, 18, 19, 20, 21, 22, 23, 24, 25, 26). The aim of the study was to highlight the existence and the prevalence of atypical forms of pandemic influenza and its clinical presentation.

Patients and method

This observational prospective study was conducted in the Infectious Diseases Hospital of the UHC "Mother Theresa" Tirana, over the period May 2009–March 2010. Laboratory confirmation of 2009 (H1N1) virus infection was performed within 2 days after patients' admission. Most A/H1N1 influenza cases meet the definition for influenza-like illness of fever plus cough or sore throat (27). AFPI were regarded patients not presented with classic influenza syndrome. Clinical signs and symptoms were described along with radiologic and arterial blood gases findings and were compared between patients with atypical and typical influenza.

Statistical Analysis

The analysis of data was carried out using SPSS 16.0 software. Continuous variables are summarized as mean ± standard deviation. Independent samples t-test was used to compate the mean age of patients. χ^2 and Fisher's exact test was used to compare the proportions between categorical variables. The p value ≥ 0.05 was considered statistically significant.

Results

52 out of 363 of cases with pandemic flu admitted at infectious diseases hospital were AFPI. The prevalence of AFPI was 14.3%, 95% CI 11.1 – 18.2. 24 cases (46.2%) were women and 28 cases (53.8%) were men. 183 patients with typical influenza were also included in the study to compare the findings between two groups. 87 cases (47.5%) of them were females and 95 cases (52.5%) were males.

Table nr.1. Clinical findings among patients with AFPI

Variable	Atypical form (n=52)		Typical form (n=183)		p
	N	%	N	%	
Age, yrs (mean-SD)	46 (± 13)		35 (± 17)		0.01
Gender					NS*
Female	24	46.2	87	47.5	
Male	28	53.8	95	52.5	
Clinical signs					
Fever	19	37.1	178	97.2	0.01
Cough	23	45.2	145	79.2	0.01
Sore throat	8	15.3	70	38.3	0.01
Rhinorhea	4	7.1	49	27.0	0.01
Headache	3	6.2	46	25.1	0.01
Fatigue	16	30.2	22	12.1	0.01
Nausea, vomiting	8	15.1	5	2.5	0.01
Diarrhea	3	5.8	10	5.5	NS
Pneumonia	33	63.5	46	25.1	0.01
ARI with fever	11	21.2	16	9.0	0.02
Septic syndrome	5	9.6	2	0.9	0.04
Encephalopathy	3	5.8	1	0.5	0.04
O_2 saturation level					
95% - 81%	15	28.8	69	37.7	NS
80% - 70%	6	11.5	3	1.6	0.01
<70%	8	15.4	1	0.5	0.01

Table nr.1. Clinical findings among patients with AFPI

Variable	Atypical form (n=52)		Typical form (n=183)		p
	N	%	N	%	
Oxygen therapy					
Facial mask	22	42.3	48	26	0.03
CPAP	4	7.7	2	1.2	0.03
Endotracheal intubation	6	11.5	5	2.7	0.02
Immune status					
Immune-competent	32	61.5	143	78.0	0.02
Diabetes	7	13.5	7	4.1	0.02
Asthma	5	9.6	4	2.2	0.03
Cardiopathy	4	7.7	2	1.3	0.03
Pregnancy	4	7.6	2	1.2	0.03
Renal transplant	1	1.9	4	2	NS

*non significant

The mean time from symptom onset to medical visit for patients with atypical form was from 3.5 days (range, 1 to 5 days), whereas for patients with typical influenza was 3.4 days (range, 1 to 10 days), without significant difference syndrome, (p =0.7).

Most patients presenting for care have typical influenza like illness with fever and cough, symptoms that are sometimes accompanied by sore throat and rhinorrhea (Table 1). Systemic symptoms are frequent. Gastrointestinal symptoms (including nausea, vomiting, and diarrhea) occur more commonly than in atypical form of influenza, with a significant difference between them.

33 cases (63.5%) of atypical influenza had a diagnosis of Pneumonia, 11 cases (21.2%) ARI with fever, 5 cases (9.6%) Septic syndrome and 3 cases (5.8%) Encephalopathy, χ^2=43.6, p < 0.01 with a significant difference with cases of typical form (Figure nr.1).

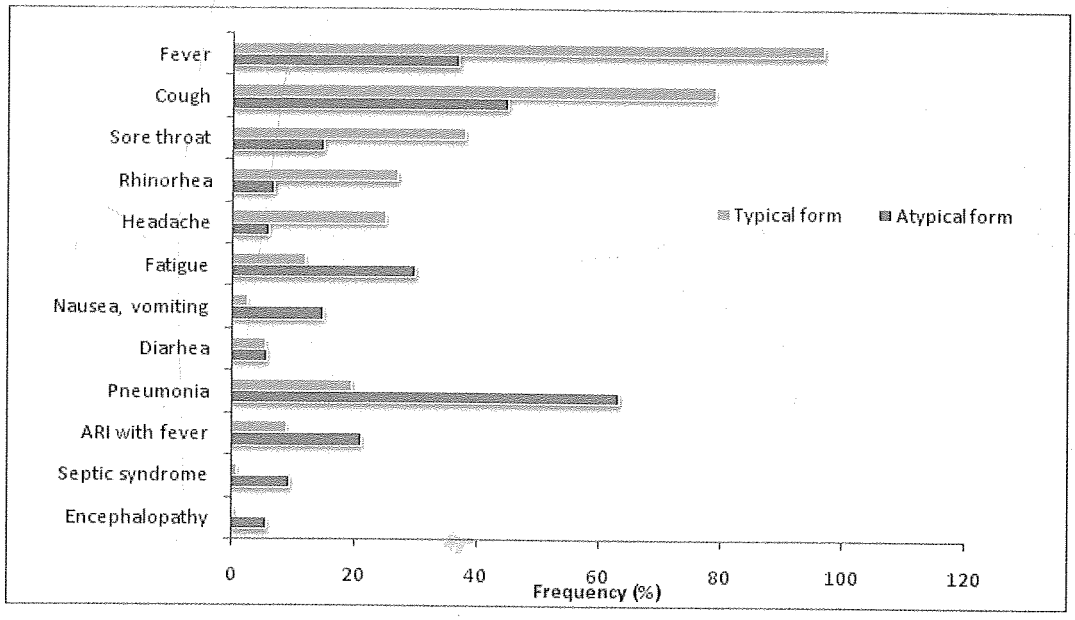

Figure nr.1. Comparison of clinical signs and symptoms among patients with typical and atypical form of influenza

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Radiographic findings: 10 cases (30.3%) out of 33 patients of atypical influenza with pneumonia presented the interstitial form, 10 patients (30.3%) presented lobar and 13 patients (39.4%) presented a mixed form of pneumonia. Patients with typical influenza presented unilateral or patchy bilateral areas of consolidation, nodular opacities, bronchial wall thickening, and small pleural effusions;

Empiric antibiotic and/or specific antiviral treatment was immediately started in all patients, according to their risk stratification, in agreement with international guidelines.

Among patients with atypical form the level of oxygen saturation during the ARI resulted in 80-95% in 15 cases; 70-80% in the 6 and under 70% in 8 cases, $\chi^2=4.6$ $p = 0.09$, (figure nr. 2).

Hypoxemia, 80% -70% and <70% was more severe among patients with atypical form with a significant difference with typical form (figure 2).

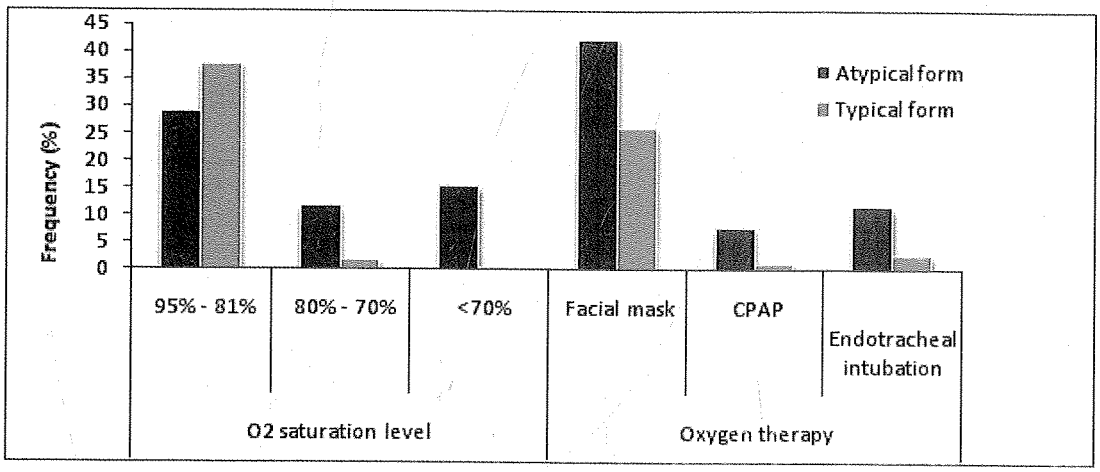

Figure nr.2. O_2 saturation level

Among patient with atypical form oxygen therapy was applied in 22 cases (42%) with facial mask; 4 cases (7.7%) with CPAP and 3 cases (5.8%) patients required endotracheal intubation, with a significant difference with patient with typical form of influenza $p < 0.01$.

The majority of patients were immune-competent, 32 cases (61.5%) of them. Out of them, 7 cases (22%) patients were obese. 20 patients (38.5%) presented with a compromised immune status.

Immune-suppression, pregnancy and diabetes, the most frequent co-morbidity has been found in 7 patients (13.5%) followed by asthma in 5 patients (9.6%), cardiopathy in 4 patients (7.7%), pregnancy in 3 patients (5.8%) and renal transplant in 1 patient (1.9%), $\chi^2=77.6$ $p < 0.01$, (figure nr.3).

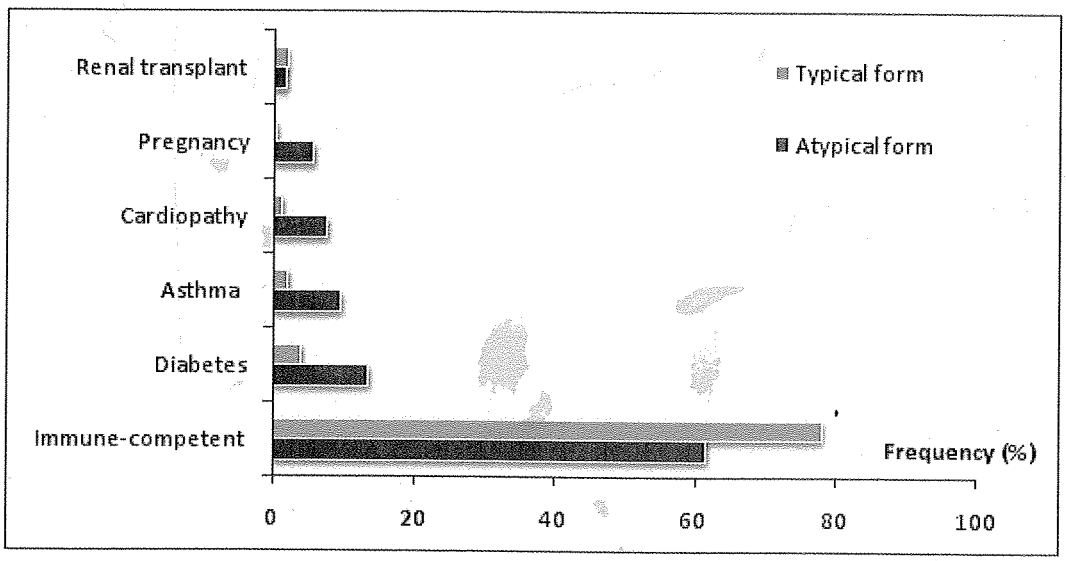

Figure nr.3. Immune status

Higher levels of lactate dehydrogenase 469.8IU/l, creatine phosphokinase 216.9IU/l, and creatinine were found among patients with atypical form of influenza. Leucopenia, lymphopenia and thrombocytopenia were common among patients with atypical for of influenza compared to other patients (table nr.2). The erythrocyte count, hemoglobin and hematocrit levels were found within normal limits in almost all patients.

Table nr.2. Laboratory results. Blood cell, hepatic and renal functional analysis of A(H1N1) patients on admission. (Mean±SD)

Biochemical and hematological parameters	Atypical form (n=52)	Typical form (n=183)	p
RBC ($x10^6$)mm^3	4.4 (±0.6)	4.5 (±0.5)	0.2
WBC ($x10^3$)	4.1(±1.9)	5.7 (±1.5)	<0.01
Lymphocyte (10^3) mm^3	0.8 (±0.3)	1.4 (±0.2)	<0.01
Platelet($x10^3$) mm^3	161.4 (± 31.5)	193.4 (± 27.4)	<0.01
ALT (IU/l)	50.8 (± 76.4)	27.5 ± 20.4	<0.01
AST (IU/l)	36.7 (± 20)	29 (±15)	<0.01
CK (UI/l)	216.9 (± 44.3)	167.2 (± 38.3)	<0.01
LDH (UI/l)	469.8 (± 322.8)	316.8 (± 259.8)	<0.01

Discussion

Findings obtained from the initial assessment of 2009 pandemic A/H1N1 virus infections are presented. Infection due to H1N1 influenza is commonly presented with flu-like symptoms, while in the severe form this may manifest as pneumonia and respiratory failure. The majority of patients in our study presented with typical influenza symptoms.

The immune status of AFPI patients was similar to that seen in patients with influenza syndrome (28, 29, 30, 31). Clinical suspicion of atypical presentations of influenza should involve pregnant women, patients with immune-suppression associated with laboratory findings. Therefore, there should be a high suspicion of severe disease in young patients presenting with clinical signs of tachypnea, hypoxemia, hypotension and/or diarrhea and high levels of lactate dehydrogenase (LDH), creatine kinase (CK) creatinine, thrombocytopenia and lymphopenia. Chest radiologic examination can provide early detection of interstitial involvement in A (H1N1) infection pneumonia (32, 33, 34, 35, 36). Its routine integration into clinical management could allow rapid identification of patients who should immediately start treatment. WBC, lymphocytes and thrombocytes, which was significantly different from that of the mildly ill patients. The lymphocytes could recover to a normal limit after the patients' condition improved, which was a significant predictor for clinical prognosis (37,38,39). Regarding the hepatic and renal functions values among severe patients were significantly higher compared to non severe patients. Recently, few cases of atypical presentation like encephalopathy due to H1N1 have been reported worldwide (40, 41, 42, 43). The underlying mechanism of encephalopathy in H1N1 infection still remains unclear, with multiple theories including host immune response and genetic susceptibility, and CSF findings are usually not helpful in the diagnosis (44,45). Our cases had late-onset encephalopathy as opposed to early-onset (within 48h) encephalopathy found in patients with influenza A and B, which may reflect different mechanism of pathogenesis (46). Also, in pandemic H1N1 influenza, frequent abnormal laboratory parameters are high lactate dehydrogenase, creatine kinase, aminotransferases and white blood cells (47,48). Although thrombocytopenia is not uncommon and may be present in up to 20% of the hospitalized patients with H1N1 influenza, severe thrombocytopenia is very infrequent (48). Our cases had atypical presentation of H1N1 influenza with encephalopathy and severe thrombocytopenia.

Because of such variable presentations of H1N1 virus, patients with viral fever, with or without flu-like symptoms, should be suspected and screened for H1N1 virus infection, especially in the presence of thrombocytopenia that could mimic dengue fever. Clinical judgment, on the basis of the patient's disease severity and progression, age, underlying medical

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conditions, likelihood of influenza, and time since onset of symptoms, is important to consider when making antiviral treatment decisions for high-risk outpatients. The bottom line is that, when clinically indicated, antiviral treatment should not wait for laboratory or radiographic confirmation of influenza.

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