

Clinical Manifestations of Influenza A-H1N1 in Hospitalized Children: About 20 Cases

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Summary

Influenza A (H1N1) 2009 is an acute contagious respiratory infection caused by the influenza A virus. Since the 2009 pandemic, influenza A H1N1 has been an annual epidemic. In the majority of cases, influenza A is mild, but it can be severe in infants and young children with chronic illnesses such as asthma. The severity of influenza depends on many factors, including the virulence of the virus strain and the level of pre-existing immunity and terrain. We report 20 confirmed cases of influenza A H1N1, collected during the period from November 1, 2018 to February 19, 2019 in the unit of pediatric pneumo-allergology of the children's hospital of CHU Ibn Rochd in Casablanca. The aim of this work is to describe the clinical, para clinical profile hospitalized. The average age was 3 years. The main reason for admission was respiratory distress found in all patients. In 50% of cases, there was a comorbidity such as asthma and acute adrenal insufficiency. The clinical picture varied from viral bronchiolitis (6 cases), moderate asthma exacerbation (5 cases), severe asthma exacerbation (6 cases), 2 clinical pictures of pneumonia and an influenza syndrome on adrenal insufficiency (1 case). Fever was present in 18 patients. Digestive signs such as diarrhea and vomiting were present in 6 cases. Three patients with asthma required intensive care. Two cases were treated with oseltamavir. The average length of hospitalization was 7.5 days, with extremes ranging from 3 to 18 days. The evolution was favorable in all cases. Influenza A H1N1 virus causes both respiratory and non-respiratory symptoms and the clinical picture may change depending on the age of the patient. The severity of the presentation is mainly related to the existence of underlying comorbidity. We conclude that preventive measures remain crucial and that influenza vaccine is highly recommended in cases of underlying morbidity.

Keywords: influenza pandemic influenza A (H1N1) v, Child, hospitalized, Infant, asthma.

Introduction

Influenza is an acute contagious respiratory infection that causes annual epidemics and some pandemics, some of which have a high mortality rate. Only influenza A and B viruses are responsible for influenza [1]. Since the emergence of influenza, A (H1N1) in 2009-2010, it represents the 4th influenza pandemic of the 20th century. The severity of influenza varies from a mild influenza-like illness to major respiratory distress, mainly in infants and young children with chronic diseases such as asthma. The severity of influenza depends on many factors, including the virulence of the virus strain, the level of pre-existing immunity, and the terrain. Children are a major reservoir of the virus and play a central role in its dissemination [2]. Symptoms are not very specific, reflecting an acute febrile respiratory illness with

inappropriate antibiotic prescriptions during influenza epidemics, from 10 to 30% [1] with sometimes longer hospitalizations.

The objectives of this study are to describe the clinical, para-clinical and evolutionary profile of the hospitalized patients.

Patients and Methods

This is a prospective and descriptive study conducted from November 1, 2018 to February 19, 2019. We included in this study any child aged less than 14 years, hospitalized for suspected acute lower respiratory infection.

We collected anamnestic, clinical, radiological and biological data in operating sheets made beforehand for

this purpose. Nasopharyngeal swabs were taken to test for influenza virus in all included children. The physicians of the department were trained to perform the nasopharyngeal swabbing in order to guarantee the good quality of the sample, which consists in bringing back secretions and infected cells in the swab. These samples were sent to the microbiology laboratory of the University Hospital.

They were subjected to gene amplification by a ready-to-use multiplex Polymerase Chain Reaction (PCR) kit for confirmation: FilmArray-Panel Respiratory. This multiplex PCR kit integrates DNA/RNA extraction from the sample, amplification and detection of 17 viruses and 3 bacteria including Influenza A and B viruses.

Results

Ninety-six patients were included in this study. The diagnosis of influenza A was confirmed in 20 of them. The average age was 3 years [3 months - 9 years]. The patients were hospitalized for different reasons: A severe exacerbation of asthma in 6 patients and a moderate exacerbation of asthma in 5 patients, with 6 cases of viral bronchiolitis, 2 clinical pictures of pneumonia and one case of acute adrenal insufficiency.

These clinical pictures were associated with signs of viral infection. Symptoms suggestive of influenza included fever, rhinorrhea, cough and sometimes digestive

disorders such as diarrhea, vomiting and abdominal pain. Three children presented with headaches.

Two-thirds of the children had a chronic disease: 11 patients with asthma and one case of acute adrenal insufficiency. Almost all patients were febrile at the time of diagnosis (18/20). This fever was greater than or equal to 39°C in 7 patients. The maximum temperature was 40.1°C.

All patients had respiratory signs in the foreground: the first respiratory sign in frequency was cough in 18 cases, followed by tachypnea in 16 cases and the third symptom represented by rhinorrhea in 14 patients. Cough and tachypnea were mainly explained by asthma exacerbation in the 11 asthmatic children and infants admitted for viral bronchiolitis.

High fever, headache, asthenia and digestive disturbances were the main reasons for suspecting influenza. Six children had, in addition to respiratory signs, digestive signs with 1 case of diarrhea, 2 cases of vomiting, 1 case of abdominal pain and 2 patients had both diarrhea and vomiting.

The clinical examination showed signs of respiratory struggle in 7 patients, pleuropulmonary auscultation showed sibilant rales in 9 cases and snoring rales in 5 cases in relation to the chronic pathology that motivated the hospitalization. (Figure 1).

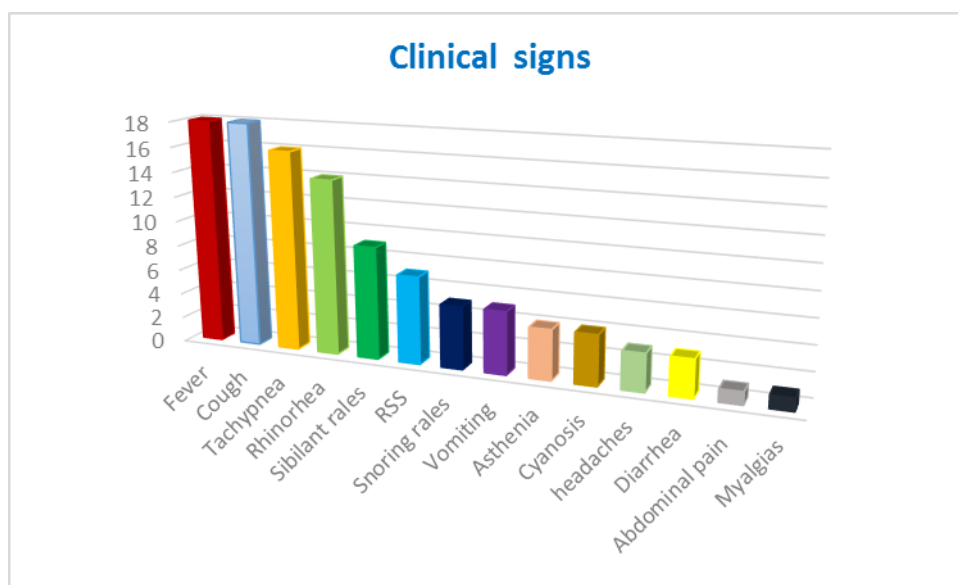


Figure1: Clinical signs of children with influenza A (Winter 2018-2019).

Biologically, 17 patients underwent a blood count: we noted an increase in the neutrophil count in 3 patients. Lymphopenia was observed in 4 patients ranging from 407 elements/mm³ to 1330 elements/mm³.

C-reactive protein (CRP) was measured in 16 patients. CRP ranged from 1 to 127mg/l. It was elevated (>30mg/l) in 5 patients.

PCR confirmed the diagnosis of H1N1 infection in 20 cases. 8 patients were identified by multiplex PCR as co-infected with other viruses as follows: 4 cases of co-

infection with Respiratory Syntycial Virus (RSV), 3 cases of co-infection with enterovirus - rhinovirus and one case of co-infection with Metapneumovirus - rhinovirus - enterovirus.

The 20 patients had benefited from a frontal chest X-ray: 4 patients had a normal chest X-ray and 16 patients had pneumonia (8 cases) of which one case was complicated by pneumomediastinum and 8 patients had a bronchial syndrome.

The complications were respiratory: three asthmatic patients who had stopped their background treatment

with poor compliance, required intensive care, one of whom was intubated and ventilated. Another patient was admitted to the ICU for severe acute asthma on two occasions with an interval of 24 hours and a total length of stay of 6 days. This child was complicated by diffuse cervical subcutaneous emphysema with

pneumomediastinum and diffuse bilateral pneumonia (Figures 2 and 3). A last asthmatic patient was readmitted to the department 48 hours after his discharge for the same symptomatology (respiratory distress, fever, asthenia). Acute dehydration, complicating vomiting and diarrhea, was noted in two patients.



Figure 2: Chest X-ray: Pneumomediastinum with bilateral alveolar foci and subcutaneous emphysema.

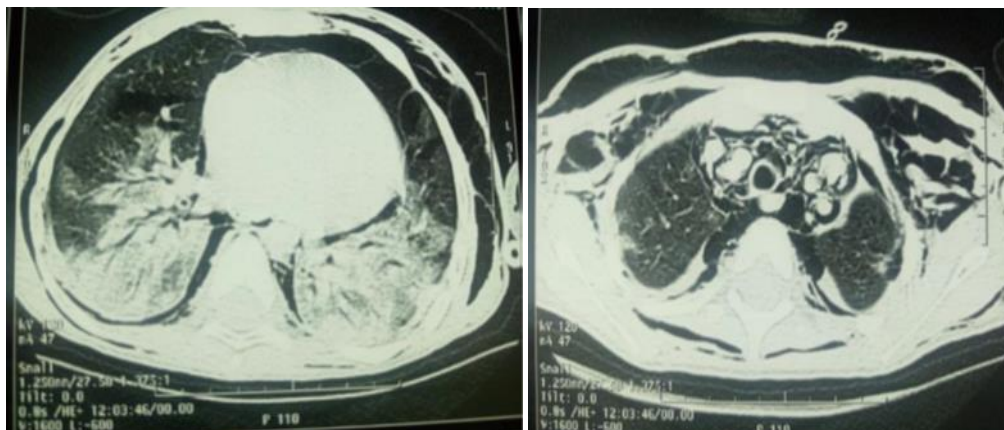


Figure 3: Chest CT: Pneumomediastinum, bilateral pneumonia and subcutaneous emphysema.

The average length of hospitalization was 7.5 days with extremes ranging from 3 to 18 days. Therapeutically, 12 patients were initially treated with amoxicillin in 9 cases and third generation cephalosporin in 4 cases. Antiviral treatment with Oseltamavir was prescribed in two patients due to the severity of their clinical picture. The evolution was favorable in all cases. No deaths were noted.

Discussion

Influenza A, H1N1 2009 is a new influenza virus pathogenic in humans. It is a variant of influenza A virus [2]. Influenza A is an extremely contagious respiratory viral disease responsible for annual epidemics of varying intensity. It is still considered as a mild disease for the rest of the population and especially for children.

The primary site of replication of influenza viruses is the nasal mucosa, but in the case of low-level infection, replication can occur throughout the respiratory tract, from the bronchi to the alveoli.

H1N1 lower respiratory tract infections can present as true viral pneumonias responsible for a severe and sometimes fatal infectious state [1].

During 2009, the world experienced an influenza pandemic related to the A (H1N1) strain [3]. Initially, the information collected in the first affected countries concerned the most severe cases and pediatric data were scarce and concerned only hospitalized children [4].

Several studies have shown that children are more affected than the general population, especially those under five years of age [5]. Its attack rate is 1.5 to 3 times higher in children [1].

The rate of hospitalization in this study appears to be very low, which cannot be compared with the risk of hospitalization in the general population, since the sample was only taken from subjects who had already been hospitalized for various reasons.

In this series, the mean age was 3 years, in agreement with a study by C. Desmoulins et al [4] where the median age was 4 years (1 day -17.5 years).

Two-thirds of the children had a chronic disease classifying them as a person at risk for influenza: the first risk factor was asthma as in all published series [4].

Respiratory pathologies represent the predominant risk factor with up to 40% of children with respiratory pathologies among those hospitalized for pandemic influenza [6,7], followed by acute adrenal insufficiency.

It was described in a study conducted in 2011 [8] that acute adrenal insufficiency frequently associates with severe respiratory infections both bacterial and viral. This is due to the similarity between certain viral amino acid sequences and those that make up ACTH. This would be responsible for the decrease in blood levels of ACTH after the activation of antiviral antibodies [8]. This humoral response is frequently associated with inhibition of adrenal glucocorticoid production and peripheral resistance to the use of these molecules.

In this study, patients were hospitalized for different reasons, namely moderate to severe asthma exacerbations, viral bronchiolitis, clinical pneumonia and acute adrenal insufficiency. Fever was the most common symptom of influenza, regardless of age. The percentage of febrile children among those hospitalized for influenza (18/20) was similar to that observed in other studies [6]. Fever was accompanied by respiratory signs with a predominance of cough in 18 patients, which is consistent with other studies where a higher percentage of children with cough was reported [5].

Tachypnea was present in 16 cases followed by rhinorrhea in 14 patients which confirms a study done in Tunis [3]. The symptoms of cough and tachypnea are biased in this study. They are essentially due to the initial clinical pictures of an asthma exacerbation or a viral bronchiolitis.

Influenza virus, regardless of serotype, is known to cause gastrointestinal distress in 40% of cases and to mimic acute gastroenteritis during epidemics [9, 10, 11]. Lister et al [5] showed a predominance of gastrointestinal disorders in patients infected with influenza A (H1N1) virus; in this series, there were digestive signs in addition to respiratory signs in 6 children, including 1 case of diarrhea, 2 cases of vomiting, 1 case of abdominal pain and 2 patients had both diarrhea and vomiting.

In a study conducted in Marseille [12] in a population of 307 adults and children, 31 of whom had a positive H1N1 CRP, the two symptoms associated with a positive CRP were cough, which had a specificity of 100% in this series, and diarrhea. We also described 3 cases with headache.

The influenza virus is also known for its neurological tropism that can cause convulsions and encephalitis, especially in children [11-13], but these were not found in this series or in another Tunisian study [3].

It seems useful to use tools for biological diagnosis. In this series, all hospitalized patients underwent a biological assessment, i.e. a blood count and/or a C-Reactive Protein (CRP), which proved a suspicion of bronchial superinfection in front of a biological inflammatory syndrome in about half of the cases. This is consistent with a Tunisian study [3].

We noted lymphopenia in 4 patients ranging from 407 to 1330 mm3. In an American study published in PIDJ on 63 patients who had a blood count: 20.6% had leukopenia (25% neutropenia and 40% lymphopenia) and 40% leukocytosis [14].

It is impossible to define the virus responsible on the basis of clinical semiology without performing an exhaustive viral search. Virological diagnosis has allowed the detection of a very broad spectrum of respiratory viruses using multiplex PCR. On a study conducted in 2012 by J.Brouard et al. the incidence of influenza A in the study population was low compared to estimates of its incidence in the general population. This may be due to the young age of the patients and the selection bias of more severe cases (Table1),[15].

	Outpatients		Inpatients		OR	IC	Total
	n	%	n	%			
N	676		345				1021
Virus							
RSV	165	24.4	185	53.6	3.6	2.7-4.7	350
Rhinoviruses	181	26.8	63	18.3	0.6	0.4-0.8	244
Coronaviruses	70	10.4	25	7.3	0.7	0.4-1.1	95
H1N1v2009	65	9.6	14	4.1	0.4	0.2-0.7	79
Parainfluenza viruses	37	5.5	23	6.7	1.2	0.7-2.1	60
Adenoviruses	36	5.3	8	2.3	0.4	0.2-0.9	44
Metapneumovirus	23	3.4	11	3.2	0.9	0.5-2	34
Positive samples	527	78	307	89	2.3	1.6-3.3	
Negative samples	149	22	38	11	0.4	0.3-0.7	
Total	676 (66.2%)		345 (33.8%)				913

Table 1: Frequency of detection of different respiratory viruses in outpatients and inpatients

In this series, multiplex PCR on nasopharyngeal swab in 96 cases was positive in 20 cases. Alveolar foci were found in 8 patients with one case of pneumomediastinum associated with bilateral alveolar foci and one case of subcutaneous emphysema requiring intensive care.

We observed co-infection with other viruses, especially 4 cases of co-infection with Respiratory Syntytial Virus (RSV), 3 cases of co-infection with enterovirus - rhinovirus, and only one case of co-infection with Metapneumovirus - rhinovirus - enterovirus.

Very low rates of co-infection have been reported in England [16], Canada [17], and the USA [18]. The rate of viral co-infection was 19%, mainly with RSV, which is consistent with this study. Similarly, there was no systematic bacteriological documentation and the diagnosis of bronchial superinfections was essentially clinical [3].

Influenza infection was often the cause of respiratory decompensation in asthmatics with poor follow-up and no background treatment or poor compliance with treatment [7]. In this study, the clinical course was marked by respiratory decompensation in 3 asthmatic patients who required intensive care, one of whom was intubated and ventilated.

Another patient was admitted to the ICU for severe acute asthma on two occasions with an interval of 24 hours and a total length of stay of 6 days, complicated by diffuse cervical subcutaneous emphysema, with pneumomediastinum and diffuse bilateral pneumonia. These 3 patients had stopped their background treatment in 2 cases and in 1 case the therapeutic compliance was poor.

Another asthmatic patient was readmitted to the department 48 hours after discharge for the same symptoms (respiratory distress, fever, asthenia).

The influenza A virus could therefore give severe forms in healthy children, but especially in children with a chronic comorbidity, i.e. asthma. Another type of complication is acute dehydration complicating vomiting and diarrhea, which was noted in two patients in this series.

This considerable rate of complications found in this study (15%) is similar to a study carried out in Argentina where the percentage of children hospitalized in intensive care units reached 21% [7,19, 20].

Similarly, the percentage of hospitalized children requiring mechanical ventilation sometimes reached 17% [7, 18, 19]. In this series, we did not note any case of death. Similarly, no excess mortality was found in children without risk factors in the United States, which is also consistent with a study done in Aquitaine where there were no deaths [6]. This also confirms that H1N1 2009 infection is not severe in young children as expected and that further studies are needed to elaborate this issue.

In contrast, a study in India found a higher number of deaths among hospitalized children aged 5-10 years but not among infants [21].

It has been shown that during an influenza epidemic there is an increase in the prescription of antibiotics. In this study, 12/20 patients had initially received oral antibiotics such as amoxicillin or third generation cephalosporin intravenously. A Canadian study showed a much wider use of antibiotics, with 80% of infants under 3 months of age and 77.8% of infants between 3 and 6 months of age being prescribed antibiotics [12].

This prescription of antibiotics could be explained by the fact that the main complication observed in this pandemic was pneumonia. This frequent and almost unavoidable complication was a source of anxiety for physicians.

Antiviral treatment with Oseltamavir is justified by the severity of the clinical picture and the coexistence of comorbidity and must be prescribed within 48 hours. In this series, antiviral treatment was prescribed only for two patients due to the severity of their clinical picture, but the third patient, who also presented a severe clinical picture, did not receive it due to the unavailability of the antiviral drug. Antiviral treatment was prescribed in two thirds of cases in a Tunisian study [3]. In a study conducted in Reunion Island, the prescription of antiviral treatment with Oseltamavir was in accordance with the recommendations of the French National Authority for Health in two thirds of cases. Risk factors other than age and signs of severity guided the initiation of antiviral treatment by physicians [5].

In view of the extent of the influenza pandemic, vaccination remains the best means of combating this pandemic, with an excellent cost-efficiency ratio. It is particularly appropriate in high-risk areas, given the high risk of complications. However, the limited availability of vaccines made it necessary to define priority groups, in particular the vaccination of these patients first and then of their family circle [6].

Awareness of influenza morbidity in children has led North American health authorities to encourage vaccination of infants aged 6 months to 2 years and all their contacts.

Vaccination of pregnant women is recommended in the second and third trimesters of pregnancy, in order to protect future babies during their first 6 months of life [22].

Most of the available inactivated trivalent vaccines can be used in children. The efficacy of these vaccines has been the subject of limited studies. These studies suggest an efficacy rate of about 60%, but there is no evidence of efficacy in infants under two years of age and no data before one year of age [23]. Influenza vaccines are authorized from the age of 6 months, a limit imposed by the absence of any efficacy or tolerance data in younger infants.

According to the WHO, two administrations of influenza vaccine at one-month intervals are required from the age of 6 months, and a single dose of influenza vaccine provides sufficient responses in children over 9 years of age [24,25].

In the United States, in 2005, vaccination of healthy infants from six months to two years of age was recommended. Since 2006, this recommendation has been extended to children aged 6 to 59 months, for whom annual vaccination is recommended [23].

In France, epidemiological data are scarce and there is no vaccination recommendation for all children despite significant influenza morbidity at this age [25].

Conclusion

Influenza A(H1N1) is the first influenza pandemic that humanity has faced with rapid international collaboration. The main characteristics of this pandemic wave allow to conclude that mortality and morbidity are low. The moderate forms are the most frequent and the virus appears less severe than expected. We conclude that preventive measures remain crucial and that influenza vaccine is highly recommended in cases of underlying morbidity.

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