Unmasking Influenza Virus Infection in Patients Attended to in the Emergency Department

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Abstract

Background: Infection by the influenza virus may pass undetected in many adult patients attended to in the emergency department because its diagnosis usually relies on clinical manifestations, which can be distorted by symptoms of a preexisting disease, superposed complications or nontypical manifestations of influenza virus infection (confusing symptoms).

Patients and Methods: We performed this observational, prospective study with an antigen detection test by indirect immunofluorescence assay (IFA) to estimate the presence of influenza virus infection in such patients. No confirmatory test was performed to validate a positive or negative IFA result. Then we compared those who were antigen positive to those who were negative and also analyzed those who were positive classified by age, comorbidity and clinical presentation. We also evaluated the use of medical and hospital resources and vaccination status.

Posterior pharynx swab specimens from 136 consecutive adult patients, 74 women and 62 men with a mean age of 68.7 ± 17.9 (range: 18–97) years attended to in the emergency department of a university hospital in Barcelona during the 1999–2000 influenza epidemic were examined. Tested patients presented either a classical influenza syndrome, a deterioration of a previous condition or any abrupt onset of symptoms without an obvious cause.

Results: Influenza A virus antigen was detected in 99 (72.8%) of the 136 patients included in the study. Confusing symptoms were present in 86 patients with laboratory-confirmed influenza and 40 of them lacked influenza syndrome. Prostration, aching and fever out of proportion to catarrhal symptoms (disproportionate prostration) and cough were independent predictors for this diagnosis (OR = 5.14; 95% CI: 1.98–13.35, p = 0.001 and OR = 4.40, 95% CI, 1.65–11.75, p = 0.03, respectively).

Among the 99 patients who tested positive, 72 were ≥ 65 years of age. This older positive group compared to the 27 also positive < 65 (non-old) had a tendency to show symptoms mediated by cytokines less frequently: malaise was present in 76.4% of the older positive patients vs 92.6% in the non-old positive ones, p = 0.07. The equivalent percentages for muscle ache were: 56.9% vs 77.8%, p = 0.06; for dysthermia: 54.2% vs 70.4%, p = 0.08; for headache: 35.2% vs 66.7%, p = 0.005, and for disproportionate prostration: 47.2% vs 66.7%, p = 0.08. Cough was more frequent in the older positive group: 94.4% vs 77.8%, p = 0.02. Older positive patients were also hospitalized and received antibiotics more frequently than the non-old positive ones: 65.3% vs 40.7%, p = 0.03 and 81.9% vs 63.0%, p = 0.046, respectively. Hospitalization was independently correlated with the presence of complications (OR = 4.5, 95% IC 1.27–15.95, p = 0.02). Patients with the highest comorbidity, evaluated with the Charlson scale, were more inadequately vaccinated than those with moderate or low comorbidity.

Conclusion: Influenza virus infection has a great and underestimated impact in the emergency department during influenza epidemics. High frequency of confusing symptoms, which overcome classical influenza syndrome in adult people with comorbidity, may explain this effect. Disproportionate prostration and cough are symptoms that independently predict its diagnosis in the global adult population, whereas in the elderly, fever and cough should arouse this suspicion whether or not they present classic symptoms. In our setting, individuals with high comorbidity are inadequately vaccinated.

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Introduction

Influenza occurs in distinct outbreaks of varying extent

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nearly every year. They are associated with an increase in mortality, excess hospitalization and a high number of outpatient encounters [1]. Such eventualities and the clinical complications of influenza depend on the characteristics of the patients who suffer it [2–4].

The diagnosis of influenza is usually based on clinical data. Laboratory tests are normally reserved for monitoring the epidemics, clinical trials and other kinds of research. This lack of laboratory confirmation makes the diagnosis of infection by the influenza virus based only on clinical parameters frequently inaccurate [5, 6]. Its manifestations may vary according to the characteristics of the population affected, especially age and comorbidity [7]. In older patients and those with comorbidity, influenza diagnosis may be missed due to symptoms of a preexisting disease exacerbated by the influenza virus infection or those of a superposed complication.

The relevance of disclosing influenza in the emergency department may be enhanced by the availability of drugs, the neuroaminidase inhibitors[8], which could reduce influenza complications [8, 9].

We performed this study in order to estimate the presence of influenza virus infection in adult patients attended to in the emergency department during the influenza season. The diagnosis of influenza was based on an indirect immunofluorescence test [10] to detect the influenza virus antigen. Then, those who were antigen positive were compared to those who were negative for distinguishing features in clinical presentation, laboratory data and hospitalization. Next, positive patients were classified in groups by age, by categories of cmorbidity and by clinical complexity. These groups were analyzed for differences in clinical manifestations, the use of medical and hospital resources, vaccination status and others.

Patients and Methods

Study Setting and Population Studied

This is an observational, prospective and systematic sampling study.

Inclusion criteria were based on age, clinical data and on the period of influenza epidemics. Patients elected for testing were 18 years of age or older. They presented one of three kinds of manifestations:

a) A classical influenza syndrome, defined by the presence of at least five of the following recognized [11] clinical characteristics: abrupt onset, fever, chills, malaise, cough, coryza, muscle aches and disproportionate prostration, aching and fever with respect to catarrhal symptoms. This disproportion was judged clinically by the physician and by the patient who was asked specifically if he noticed great prostration, aching and fever with respect to his catarrhal symptoms.

b) A deterioration of a previous condition, such as chronic respiratory diseases, dementia, heart failure, diabetes and ischemic coronary heart disease.

c) Abrupt onset of symptoms like dyspnea, delirium, falls, syncope, vomiting and incontinence.

With either inclusion criteria b or c, an obvious cause of their symptoms different from influenza virus infection was ruled out by examination and basic screening tests.

The influenza epidemic period was established from data from the local virologic surveillance network of the microbiology department, which systematically performs viral antigen detection throughout the year and alerts when an influenza epidemic breaks out and finishes. During the study period, the laboratory of this department performed 953 tests for influenza virus antigen detection, of which 422 (44.3%) were positive, 421 for influenza A virus and one for influenza B. The percentages of influenza A and influenza B during this outbreak in Barcelona were: 95.2% and 0.3%, respectively. The rest were for respiratory syncytial virus: 3.4%, parinfluenza: 0.7% and adenovirus: 0.3%. The subtypes were H3N2 and H1N1, which matched the vaccine used in the immediately preceding vaccination campaign [12].

Study Setting

The study was carried out in the Adult Internal Medicine Section of the emergency department, in a tertiary care hospital: University Hospital of Santa Creu and Sant Pau in Barcelona. This hospital provides care to a population of 400,000 people. The emergency department receives patients with a wide range of gravity of their conditions, from those able to walk to seriously ill patients transported by emergency mobile units.

Study Period

The first patient was studied on December 28, 1999 and the last on February 11, 2000.

Enrollment Procedure and Number of Patients Recruited

Before the influenza epidemic was declared, consultants in the Adult Internal Medicine Section of the emergency department were instructed about the aforementioned inclusion criteria and the procedure to obtain the throat swab samples. One author was responsible for the coordination between the microbiology laboratory and the emergency department and for monitoring the patients to obtain data about their outcomes.

At the end of the enrollment period, 136 consecutive adult (≥ 18 years) patients, 74 (54.4%) women and 62 (45.6%) men, with a mean age of 68.7 ± 17.9 (range: 18–97) years had been recruited. 93 of them (68.4%) were ≥ 65 years of age.

Laboratory Procedure

Epithelial cells were collected by firmly swabbing the posterior pharynx, which provided a valid sample for influenza virus antigen detection [13–15]. Immediately after collection, the throat swab was introduced in a tub with 1–2 ml of sterile saline solution and swirled vigorously to ensure that the maximum number of cells was obtained. Liquid was thoroughly removed from the swab by pressing it against the tub wall. The remainder of the swab was discarded. 30 ml of the processed specimen were deposited in the well of a slide, and the slide was air dried and fixed in acetone for 10 min. Mouse monoclonal antibody against influenza A, influenza B, parainfluenza, respiratory syncytial virus and adenovirus was applied to each well on the slide containing specimen and it was incubated in a humid chamber for 30 min at 37 ºC. After washing, a fluorescein-labeled antibody directed against the initial antibody was added. The slide was incubated and washed as before. After drying each slide, they were viewed by fluorescence microscopy [10].

The mouse antibodies and the positive and negative controls, which consisted of cells infected and noninfected by each of the

viruses tested were provided by Chemicon International Inc. (Temecula, CA, USA).

The sensitivity of indirect immunofluorescence assay for influenza is highest during the viral replication and shedding phase of the illness. The viral shedding starts during the first 24 h following influenza virus inoculation and continues until day 6–7. As the clinical incubation period ranges from 18 to 72 h, the test is usually negative by the 5th day after the clinical onset of influenza [16]. Sensitivity ranges from 60% to 100% [17–20], depending on the reagents used and on the subtype of influenza virus circulating [12]. Specificity has been fixed at 92% [18], 97% [17], 98.7% [21] and 100% [19, 22]. Some authors affirm that this procedure is specific enough to make it unnecessary to confirm results using other techniques [19, 22]. Furthermore, some conclude that indirect immunofluorescence assay is more specific than culture [14]. It is generally accepted that throat swabs give less sensitivity than nasopharyngeal aspirates. However, this technique has some inherent difficulties, including inconvenience of collection, propensity to induce trauma and the risk that excess mucous may interfere with fluorescent antibody staining. On the contrary, exfoliated epithelial cells derived from the upper respiratory tract may be a more practical and less invasive source of diagnostic material [14]. Indirect immunofluorescence assay rapid diagnosis provides results within a clinically relevant time frame [21, 23].

Medical Data

Data on patients' acute illnesses were retrieved on admission and included demographics, clinical presentation, total leukocyte count, comorbidity, vaccination status, prescribed medications, emergency room visits, hospital admissions and discharges and visits to outpatient clinics.

Follow-up data were obtained from interviews, clinical reports, the hospital database, telephone calls and mail questionnaires, when appropriate.

Study Outcomes

Complications, hospitalization, antibiotics, symptomatic treatment, supportive therapy and evolution were the outcomes evaluated.

We considered as complications attributable to influenza any exacerbation or relapse of a preexisting disease coinciding with active influenza or any of the morbid processes that are recognized as complications of influenza. These processes are long-lasting – longer than the resolution of the rest of the symptoms – purulent bronchitis, pneumonia, sinusitis, otitis media and Reye's syndrome [7, 24, 25]. Any other disorder that coincided with or followed influenza in a period not longer than a week was also considered as a complication attributable to influenza.

We defined as supportive therapy any treatment administered to the patients, other than their previous or habitual one, to overcome the complications linked to the influenza process, or any previous medicine that required a change in dosage. Antibiotics were considered separately. Any therapy intended to mitigate influenza symptoms or its complications without a curative effect was considered as symptomatic treatment. We also recorded specific antiviral treatment.

Determination of Comorbidity

Comorbidity was classified according to the Charlson scale. It was considered absent for score 0 on this scale, low for score I or II, moderate for score III or IV and severe for score V [26].

Data Analyses

All data were double-entered into a computer and verified for accuracy. Unrecorded variables were coded as missing. Quantitative variables – age, temperature, total leukocyte count, hospital stay and duration of the process – were analyzed as means and standard deviations. Viral antigen detection, age-group, comorbidity, clinical antecedents and manifestations, vaccination, complica-

Table 1
Clinical presenting symptoms of patients with influenza A virus antigen, according to age.

	≥ 65 years			< 65 years			P-value
	Yes, N	No, N	%	Yes, N	No, N	%	
Fever	66	5	93.0	25	1	96.2	0.6
Cough	68	4	94.4	21	6	77.8	0.02
Malaise	55	17	76.4	25	2	92.6	0.07
Abrupt onset	47	25	65.3	19	8	70.4	0.6
Muscular ache	41	31	56.9	21	6	77.8	0.06
Chills	40	32	55.6	18	9	66.7	0.3
Dysthermia	39	33	54.2	19	8	70.4	0.08
Disproportionate prostration [a]	34	38	47.2	18	9	66.7	0.08
Coryza	36	36	50.0	12	15	44.4	0.6
Dyspnea	35	37	48.6	11	16	40.7	0.5
Headache	25	46	35.2	18	9	66.7	0.005
Sore throat	26	46	36.1	13	14	48.2	0.3
Thoracic pain	18	54	25.0	13	14	48.2	0.03
Conjunctivitis	12	60	16.7	7	20	25.9	0.3
Delirium [b]	7	65	9.7	4	23	14.8	0.5
Falls [b]	6	66	8.3	1	26	3.7	0.4

Yes and No: the presence of the listed symptoms. N: no. of patients who presented these symptoms. [a] disproportionate prostration, aching and fever with respect to catarrhal symptoms; [b] initially presenting symptoms only. There were more patients (Table 3) who presented these symptoms during the influenza process but not as the initial manifestation. These cases are considered complications.

tions, hospitalization, antibiotics, supportive therapy and symptomatic treatment composed qualitative variables. They were analyzed as percentages and number of cases. Differences in means of normally distributed variables were compared with the t-test; non-normally distributed variables were compared with the Mann-Whitney test. Comparison of qualitative variables was determined using the χ^2 test. Detection of independent clinical variables to predict the diagnosis of influenza virus infection was made with logistic regression multivariate analysis. Additionally, the likelihood estimate of the odds ratio was calculated using logistic regression with the conditional elimination procedure [27]. The criteria for entry/retention in the logistic model were: PIN = 0.05 and POUT = 0.10. The goodness of fit of the logistic regression model was tested with the Hosmer-Lemeshow test [28].

$P < 0.05$ (two sided) was considered statistically significant. Logistic regression was performed with the SPSS 010.0 for Windows statistical package (SPSS Inc., Chicago). The rest of the statistics was analyzed with the StatView 4.5 for Macintosh package (Abacus Concepts, Inc. California).

Results

The influenza A virus antigen was detected in 99 (72.8%) of 136 recruited patients. No patient presented influenza B. There were differences between patients who tested positive and those who were negative in terms of clinical manifestations, laboratory data and hospitalization. Clinical differences were fever: 93.8% vs 80.0%, p = 0.02; cough: 89.9 vs 64.9%, p = 0.0005; muscular ache: 62.6% vs 40.5%, p = 0.02; chills: 58.6% vs 37.8%, p = 0.03, dysthermia 58.6% vs 40.5%, p = 0.06; and disproportionate prostration, aching and fever with respect to catarrhal symptoms: 52.5% vs 18.9%, p = 0.0004. Disproportionate prostration and cough were independent predictors for the diagnosis of influenza: OR = 5.14; 95% CI: 1.98–13.35, p = 0.001 and OR = 4.40, 95% CI, 1.65–11.75, p = 0.03, respectively. Total leukocyte count was higher in patients with a negative test for the influenza antigen (11,066 ± 4,880 vs 8,897 ± 3,708 × 10^9/l, p = 0.03).

Among the 99 patients who tested positive, there were significant differences according to their age and comorbidity. Clinical differences between patients 65 years or older and those younger than 65 are shown in table 1. In addition, older patients were hospitalized, had complications, and received antibiotics significantly more frequently: 65.3% vs 40.5%, p = 0.03, 63.8% vs 38.5%, p = 0.03, and 81.9% vs 63.0%, p = 0.046, than younger ones. The variations with reference to comorbidity, which was classified according to the Charlson scale, are presented in table 2. Patients with a background of lung disease also suffered complications, received antibiotics and supportive therapy signifi-

Table 2
Hospitalization, clinical symptoms, vaccination, systemic corticoids and paracetamol prescription, related to comorbidity in patients with influenza A virus infection.

Comorbidity	Hospitalization	Complicated influenza	Delirium	Vaccinated / not vaccinated but indicated / not vaccinated and not indicated	Corticoids	Paracetamol
Absent	27.8	61.1	0.0	22.2 / 33.3 / 44.4	0.0	83.3
Low	52.9	85.3	5.9	32.4 / 55.9 / 11.8	35.3	47.1
Moderate	75.7	89.2	24.3	55.6 / 38.9 / 5.6	45.9	54.1
Severe	70.0	100.0	20.0	30.0 / 70.0 / 0	40.0	40.0
P-value	0.005	0.02	0.03	0.001	0.008	0.04

Table 3
Different manifestations of influenza and percentage of positive tests for Influenza A virus antigen.

	Presence of influenza syndrome		Absence of influenza syndrome	
	No.[a]	Influenza A virus, %	No.[a]	Influenza A virus, %
Complex presentation: presence of symptoms of a preexisting disease and/or of superposed complications and/or atypical manifestation	55	83.6	64	62.5
Simple presentation: patients without symptoms of a preexisting disease and/or of superposed complications and/or atypical manifestations	10	90.0	3	66.7
All patients [a]	65	84.6	67	62.3

[a] the presence of a typical influenza syndrome was fully evaluated in 132 of the 136 patients

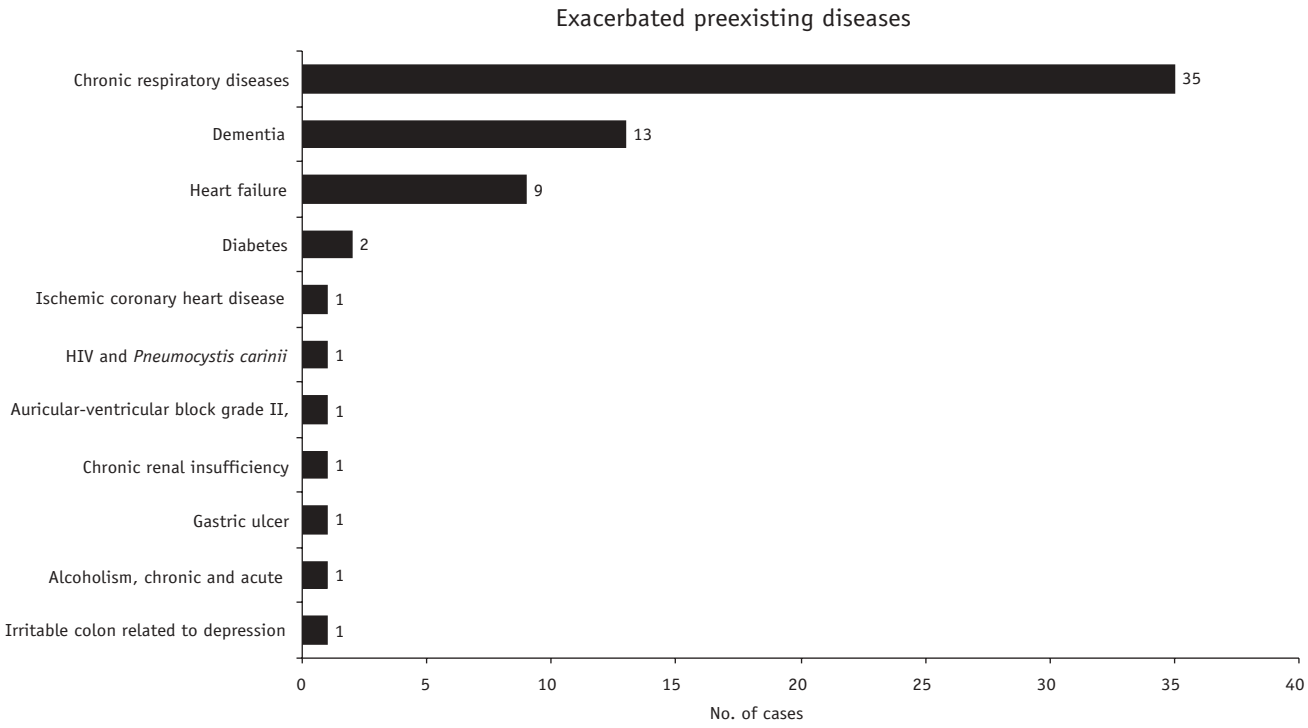

Figure 1. Number of patients who presented symptoms of a range of exacerbated preexisting diseases.

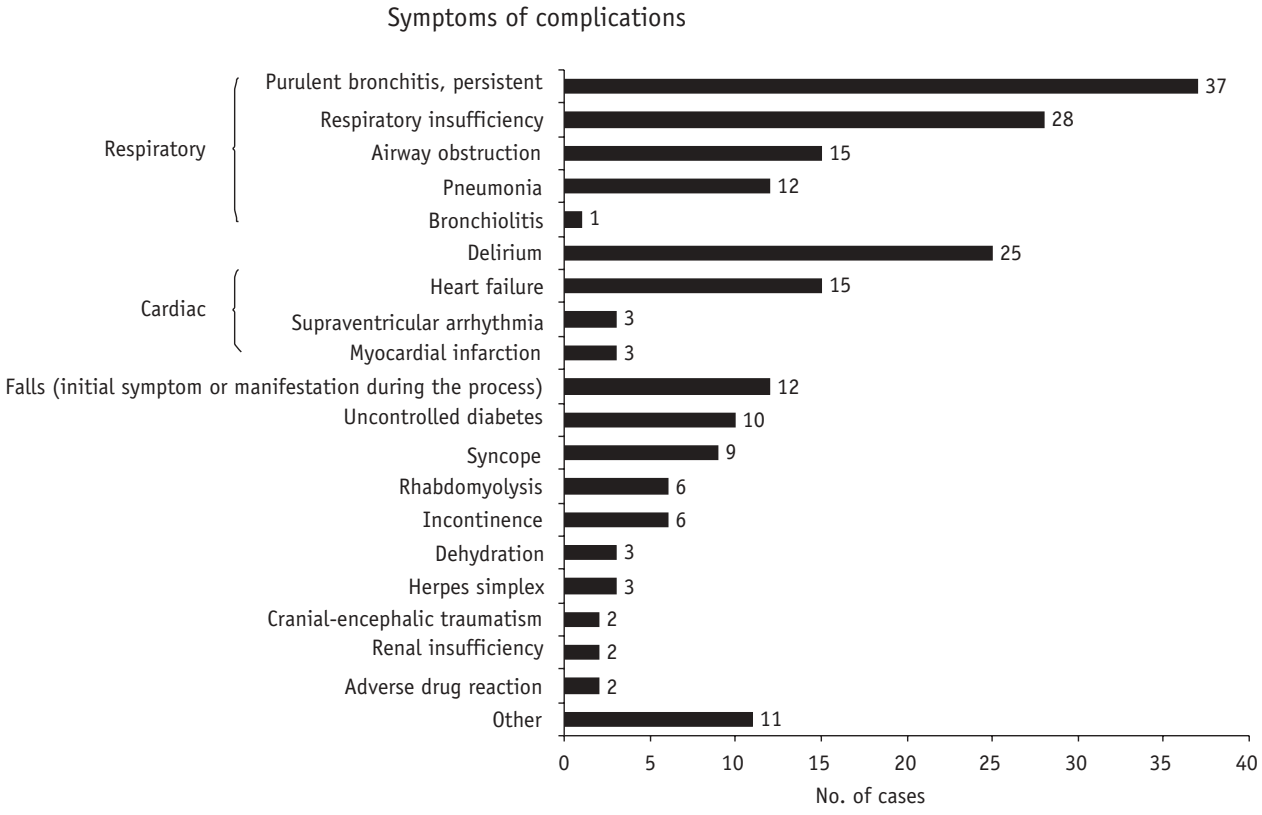

Figure 2. Patients who presented symptoms of an assortment of superposed complications.

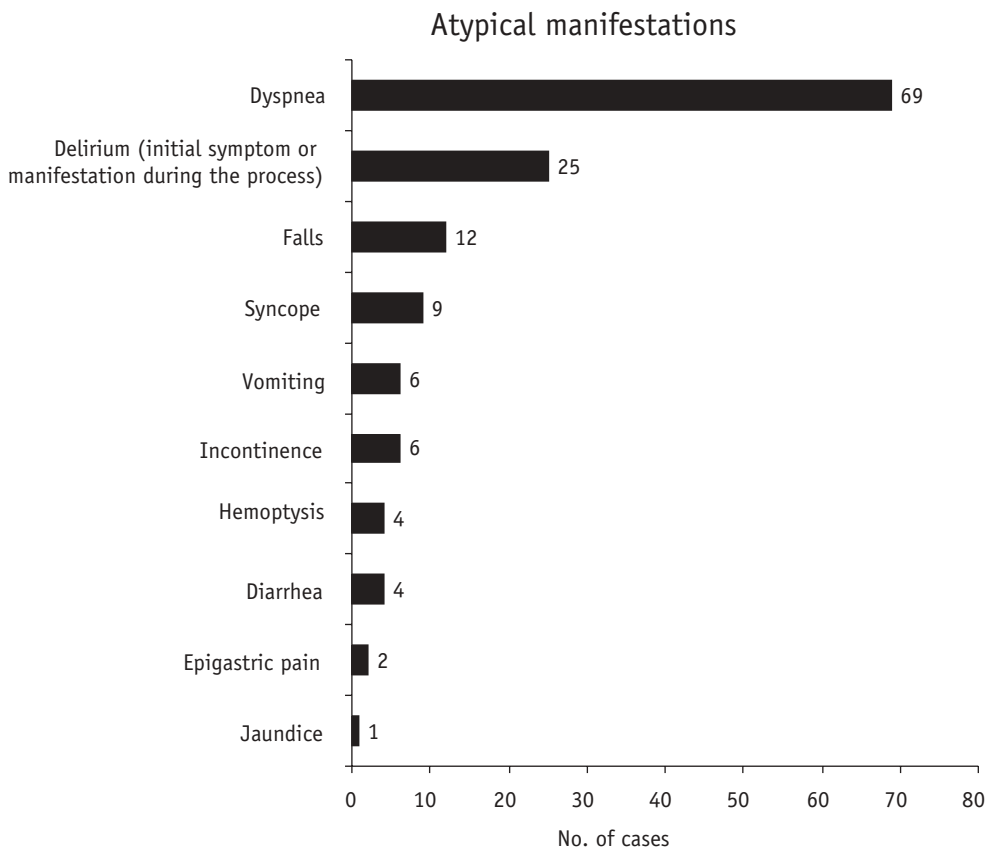

Figure 3. Patients who presented diverse atypical manifestations.

cantly more often than those without (38.5% vs 7.7%, p = 0.003; 90.0% vs 63.3, p = 0.002; 94.0 vs 49.0 p = 0.0001).

Table 3 shows the percentages of positive testing among patients grouped in two categories of clinical presentation: complex and simple, and for all patients, each group split according to the existence or nonexistence of a classical influenza syndrome as defined by us.

Complex presentation in table 3 refers to the presence of symptoms of a preexisting disease and/or the presence of superposed complications and/or of atypical manifestations. The frequency and distribution of these symptoms are shown in figures 1, 2 and 3. Note that the sum of the exacerbated preexisting diseases, complications and atypical manifestations yields more than 119 cases because many patients had more than one of these manifestations.

54 patients of those who tested positive (40.0%) were admitted to the hospital; the remainder were treated and monitored as outpatients. The majority of hospitalized patients were, in addition to the elderly, those with comorbidity (Table 2) and those with complications (65.1% vs 25.0%, p = 0.003). Among age, comorbidity and presence of complications, only the latter was independently correlated with hospitalization (OR = 4.5, 95% IC 1.27–15.95, p = 0.02).

Vaccine had been given to 33.6% of the patients in whom the influenza virus antigen was detected. Patients aged 65 years or older had been vaccinated significantly more frequently than those who were younger, 47.9% vs 14.8%, p = 0.003, (OR = 5.28, 95% IC 1.55–22.81, p = 0.006). The rate of vaccination in the groups defined by the comorbidity index is shown in table 3.

Seven patients (7.1%) received specific antiviral therapy with amantadine.

We did not find significant differences in the course of illness between vaccinated and unvaccinated people or between those treated and untreated with amantadine.

Two patients, a man aged 91 and a woman aged 97, died. The man had received vaccine. The overall mortality rate was 2.0%.

Discussion

A high percentage of patients included in our study had a positive test for the detection of influenza A virus. Many of them had superposed manifestations and, of these, a lot did not fulfill the criteria for clinical diagnosis of influenza virus infection. This is relevant because such patients are probably undiagnosed in routine practice.

The high percentage of positive tests in our patients contrasts with the low one (44.3%) in the surveillance network. As both populations were studied by the same method and by the same technicians and the test specificity is very high [14,17–19, 21], this difference cannot be attributed to false-positive results. It may be better explained by differences in the population tested and the aim of testing in each case. While we studied exclusively adult patients to determine the impact of influenza virus infection in the emergency department, the network surveillance tests the pediatric population in order to alert the community to the beginning of an influenza epidemic.

The absence of influenza B in our study was in concordance with the extremely low incidence of influenza B in Barcelona during the 1999–2000 epidemic [12].

The significant clinical differences we found between patients who tested positive and those who were negative

must be cautiously considered. The sensitivity of indirect immunofluorescence assay is variable and a negative test does not rule out an influenza virus infection. Therefore, the negative group may have been contaminated with patients who were in fact infected with influenza virus. However, the high percentage of positive patients in our study may indirectly imply that the sensitivity was high. In contrast, the comparisons within the positive patients classified in groups by age, by categories of comorbidity and by clinical complexity are very reliable due to the high specificity of indirect immunofluorescence assay [14, 17–19, 21].

We found a high frequency of classical influenza manifestations in the patients in whom the influenza virus antigen was detected. Cough and disproportionate prostration to catarrhal symptoms were independent predictors for influenza virus infection. We coincide with other studies [5, 6] in considering cough as an independent predictor for influenza diagnosis but we add disproportionate prostration and we differ in fever, which was not an independent predictor in our study.

Leukocyte count was significantly lower in patients with a laboratory-confirmed influenza diagnosis, which is concordant with reported information [11].

It is relevant that many symptoms, except fever, that are mediated by cytokines: malaise, muscle ache, dysthermia, disproportionate prostration and headache [29], were less common, and some significantly less common, in the population ≥ 65. Interestingly, the bronchial symptom of cough was more frequent in patients aged 65 or older. Therefore, we might conclude that people 65 or older who present fever and cough during the influenza season probably suffer influenza virus infection, whether or not they have other classical influenza symptoms. This is important because according to many observations [7, 30], including ours, influenza virus infection is detrimental in older people [31]. They frequently require hospitalization, which dramatically increases costs [4]. This increase has been quantified in a multiplicative factor of 22.9 [32]. Therefore, every effort made to prevent influenza or to attenuate it in older people should result in a significant reduction in health costs.

There are few recently published studies that consider the consequences of patients' comorbidity and preexisting diseases in influenza virus infection behavior. In our experience, the Charlson scale degree of comorbidity [26] has been useful in discriminating between some aspects of influenza virus infection presentation. Complications, atypical symptoms, hospitalization and supportive therapy were more frequent in people with high comorbidity. Contrarily, symptomatic treatment was given more frequently to patients without or with low comorbidity. In our patients, having a previous pneumopathy was a significant handicap for suffering influenza virus infection. A higher risk of bronchitis complicating influenza in these patients has been reported [24]. As bronchitis may be considered an inherent manifestation of influenza virus infection, we considered this symptom as a complication only when it persisted after the resolution of the rest of the symptoms.

It is relevant that people with the highest comorbidity on the Charlson scale [26] and thus with a great risk of developing complications if infected by the influenza virus, lacked vaccination. Perhaps they did not receive it due to difficulties in mobilization and attending the outpatient clinics where vaccination is normally administered. Nevertheless, it is a failure of vaccine delivery. As there is ample agreement on the utility of vaccination in patients with comorbidity [24, 33], an effort to detect such patients and to vaccinate them should be considered [34–36].

Although we did not find differences between vaccinated and unvaccinated people despite the good match between the prescribed vaccine and the circulating subtypes of the influenza virus that season, this does not mean that vaccination is not protective. This may be explained by the fact that people for whom the vaccine had been protective did not come to the hospital.

Only seven positive patients received specific treatment with amantadine. However, we consider that the prescription of this drug and the newer neuroaminidase inhibitors, zanamivir [9, 37–39] and oseltamivir [8, 40], which can probably reduce its complications [8], should be considered in the patients we refer to in this study.

The two deaths occurred in patients who tested positive for influenza A virus. They were far older than estimated life expectancy and both had respiratory complications, two facts that increase mortality in this infection [31].

In conclusion, the incidence and impact of influenza virus infection in adult patients attended to in the hospital emergency department during influenza epidemics are probably underestimated. This is particularly relevant with the emergence of severe acute respiratory syndrome (SARS), which has many similarities with influenza virus infection in terms of etiopathology and even mortality, especially when compared to the most lethal influenza epidemics [41]. Influenza virus infection should be suspected in older people who have cough and fever during the influenza season, whether or not they have other classic symptoms. The lack of vaccination in patients with the highest comorbidity deserves consideration in regard to vaccine delivery. So does the possibility of introducing specific anti-influenza virus therapy in patients diagnosed in this way in the emergency department. With the advent of more sensitive rapid influenza diagnostic tests [42, 43] and the availability of new therapeutic agents, perhaps many cases which are undetected could benefit from specific antiviral therapy.

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