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ORIGINAL PAPER

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Comparison of clinical characteristics of influenza and respiratory syncytial virus infection in hospitalised children and adolescents

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Abstract While significant morbidity due to respiratory syncytial virus (RSV) infection in the paediatric population has been well acknowledged, little is known about the burden of influenza in primarily healthy children in Europe. In our institution, a University Children's Hospital in Switzerland, medical staff were encouraged to take nasopharyngeal specimens for multiplex polymerase chain reaction assays for influenza A and B, RSV and several other pathogens from patients hospitalised with respiratory symptoms. We took advantage of this strategy and performed a retrospective study to compare specific characteristics of influenza virus infections with those of RSV during two consecutive winter seasons. Overall, 126 patients were positive for RSV and 60 patients were positive for influenza (type A: 45; type B: 15). The median age of children with RSV, influenza A, and influenza B infection was 4 months; 2 years and 4 months; and 6 years and 2 months, respectively ($P < 0.001$). Fever and cough predominated in children with influenza infection whereas cough, rhinorrhoea, feeding difficulties and dyspnoea were the major symptoms in children with RSV infection. Of patients with influenza, 41% suffered from lower respiratory tract infection compared to 91% of those with RSV infection ($P < 0.001$). Of 60 patients hospitalised with influenza, 12 (20%) experienced febrile convulsions. None of the patients with influenza had been immunised in the respective winter season, although 27% of them had at least one underlying medical condition that would have counted as an indication for immunisation in Switzerland. *Conclusion*: Influenza virus infections, like respiratory syncytial virus infections, are a major cause of hospitalisation in children with respiratory illness during the winter season. Since it is impossible to make an aetiological diagnosis on clinical grounds, it is important to apply specific diagnostic tools in children hospitalised with respiratory illness in order to better characterise the relative burden of disease caused by the respective agents.

Keywords Children · Hospitalisation · Influenza · Respiratory syncytial virus

Abbreviations LRTI: lower respiratory tract infection · NPS: nasopharyngeal specimens · RAT: rapid antigen test · RSV: respiratory syncytial virus

Introduction

Influenza causes significant morbidity and mortality in elderly people [22] and in chronically ill patients at any age [6, 10, 18]. The burden of influenza in primarily healthy children and adolescents is less clear [6, 10, 18], although it has long been recognised that acute viral respiratory tract infections are a common reason for hospitalisation in children [17, 22]. Among these, respiratory syncytial virus (RSV) is considered to be most important as it causes yearly outbreaks of lower respiratory tract infections (LRTIs), such as bronchiolitis and pneumonia, primarily in young infants [2, 11, 12, 18]. Recently, several investigations have drawn attention to the role of influenza in hospitalised children in the United States [12, 17, 18] but only limited data are available on the clinical characteristics of influenza infection in children and adolescents in Europe [4, 15, 20, 23, 24, 25]. This may at least be partly explained by the lack of widely available, sensitive diagnostic tools for influenza virus infection and the fact that circulation of influenza viruses and RSV frequently overlaps in winter, making it difficult to separate these two agents as a cause of respiratory infection [6, 18, 20].

This work forms the medical thesis of Susanne Meury at the Medical Faculty, University of Basel, Switzerland.

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The aim of this study was to assess the clinical characteristics of influenza virus infection in comparison with RSV in immunocompetent hospitalised children and adolescents. We chose a 2-year period to account for the biannual pattern of RSV outbreaks in Switzerland [8].

Subjects and methods

Subjects

Our hospital provides general and specialised services for the paediatric population in the northwest of Switzerland. During the study period, an average of 55,735 children lived in the two cantons of the Basel area (according to population statistics assessed in December 2001 and December 2002). Until 2000, we used a rapid antigen test (RAT) for diagnosis of RSV from nasopharyngeal specimens (NPS). Starting in 2001, NPS for multiplex PCR (see below) was collected from patients hospitalised with respiratory symptoms during the cold season (October to April). Continuous and/or additional use of the antigen test for RSV was left to the treating physician's discretion.

Virology

NPS were collected on admission and sent to the virology laboratory of our hospital where RAT and/or PCR tests were performed as ordered by the physician. The multiplex PCR was designed to amplify cDNA specific for RSV, parainfluenza virus types 1 and 3, influenza A and B, and adenovirus by use of primers as previously described [7, 9, 13, 16, 19] and has undergone comprehensive in-house evaluation. All laboratory personnel were unaware of any clinical information on the respective patients. Results were usually available within 24 to 48 h. The RAT for RSV (Abbott Test Pack RSV, Abbott Diagnostic Division, Cham, Switzerland) was performed according to the manufacturers' instructions and results were available the same day.

Data analyses

Cases were identified by evaluating patient records and the virology laboratory's log books. Immunocompromised patients and those with nosocomial infections were excluded. Characteristics of patients with any positive test were extracted from their records.

Statistical analyses

Comparisons of percentages were performed by use of the chi-squared test and those of mean values by the Mann-Whitney U-test.

Results

Study population

During the study period, 653 eligible patients were hospitalised with respiratory illnesses. None of them had received influenza immunisations. The following analyses are based on 422 (65%) patients from whom NPS were obtained. Of these, 154 and 268 were hospitalised during study years 1 and 2.

The virology findings are presented in Table 1 and the seasonal distribution of cases in Fig. 1. In the winter of 2001/2002, the first cases of influenza and RSV infections leading to hospitalisation did not occur before January and the two epidemics overlapped. In contrast, in the following winter the RSV season started in October whereas the influenza epidemic occurred as late as February. RSV and influenza virus infections were similarly frequent in the 2001/2002 season whereas in 2002/2003 RSV predominated over influenza. Overall, influenza virus type A infections were more frequent than those caused by type B (45 versus 15).

Eight double infections were detected: three patients tested positive for influenza A and RSV, two for adenovirus and RSV, one for *Mycoplasma pneumoniae* and RSV, one for parainfluenza type 3 and RSV, and one for influenza B and adenovirus. Since it is impossible

Table 1 Diagnostic tests and results in patients hospitalised with respiratory tract infections

Season and test	RSV Positive (*n*)/tested (*n*); (% positive)	Influenza A Positive (*n*)/tested (*n*);(% positive)	Influenza B Positive (*n*)/tested (*n*);(% positive)
2001/2002			
PCR	23/110 (21%)	24/112 (21%)	3/112 (3%)
RAT	22/86 (26%)	Not applicable	Not applicable
Any	35/150 (23%)	24/112 (21%)	3/112 (3%)
2002/2003			
PCR	73/242 (30%)	21/226 (9%)	12/226 (5%)
RAT	61/155 (39%)	Not applicable	Not applicable
Any	91/267 (34%)	21/226 (9%)	12/226 (5%)
Total (Any)	126/417 (30%)	45/338 (13%)	15/338 (4%)

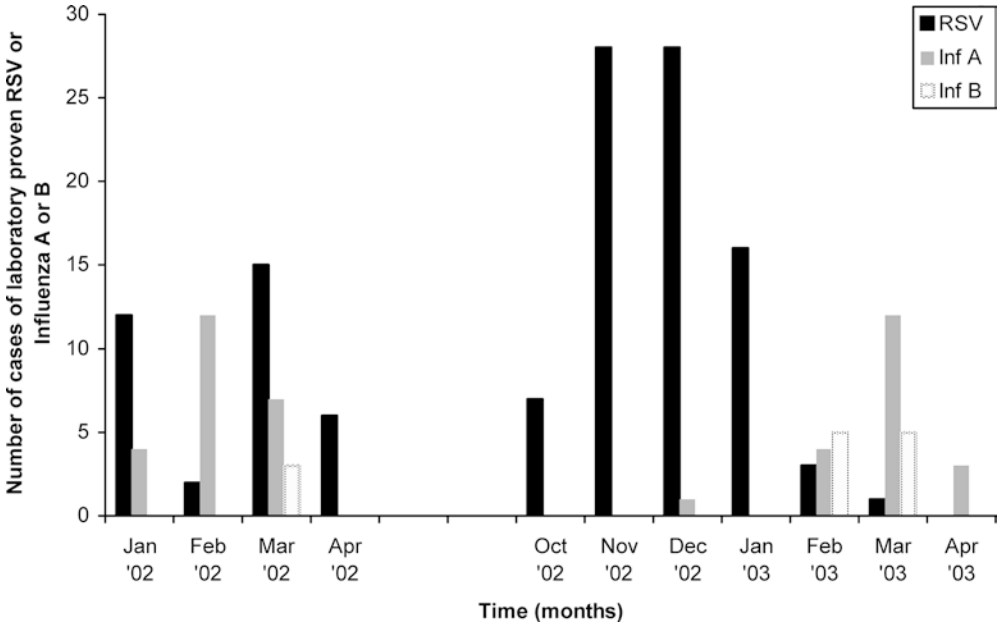

Fig. 1 Monthly hospitalisation rates for RSV and influenza A and B virus infections

to estimate the contribution of the respective organism to the patient's characteristics of illness, these cases were excluded from the following comparisons.

The median age of patients with RSV infection was 4 months (interquartile range 54 days to 1 year; 56% male) and that of patients with influenza A and B virus infections was 2 years and 4 months (interquartile range 1 year to 3 years and 1 month; 52% male) and 6 years and 2 months (interquartile range 4 years and 8 months to 9 years and 6 months; 71% male), respectively. Among patients with RSV, influenza A and B virus infections, 97%, 88% and 50%, respectively, were <6 years of age ($P<0.001$ for RSV versus influenza). Of 56 patients hospitalised with influenza infection only, 44 lived in the two cantons of the Basel area. Overall, the yearly population-based hospitalisation rate for influenza per 100,000 children (0–18 years) in Basel was 39.5 and that for children <6 years of age was 141.

Median duration of hospitalisation in patients with RSV, influenza A and B infection was 5 days (interquartile range 3–8 days), 4 days (interquartile range 3–6 days) and 3 days (interquartile range 2–4 days) and total numbers of hospital days were 718, 94 and 42 days, respectively ($P<0.001$ for RSV versus influenza) compared to a total of 1,222 days in patients with negative tests.

Clinical characteristics

Table 2 shows the major clinical diagnoses at the time of admittance and signs, symptoms and complications of patients by causative viral infection. A clinical diagnosis of LRTI was established in 41% of patients with influenza virus infection compared to 91% of those with RSV infection ($P<0.001$). Two patients with influenza B virus infection suffered from myositis which led to hospitalisation. No deaths occurred. Of 119 patients with RSV infections, 10 (8%) compared to 2 (4%) of 56 patients with influenza ($P=0.2$) required intensive care treatment during the course of their illness. Nine of those patients were infants (all with RSV infection). Interestingly, 11 (20%) patients with influenza compared to two (2%) with RSV ($P<0.001$) experienced febrile convulsions as a complication of their illness and this was the primary reason for hospitalisation in all of them. Less than 30% of patients had underlying conditions (Table 3).

Laboratory findings

WBCs and CRP levels were determined in most patients. Leukocytosis was uncommon with a trend towards a more frequent occurrence in patients with RSV than with influenza (20% versus 9% $>15{,}000/\mu l$; $P=0.06$). CRP levels were not or only slightly increased in the great majority of patients irrespective of viral aetiology.

Discussion

An intensified laboratory surveillance for influenza and RSV infections enabled us to characterise the impact of hospitalised influenza and RSV infections in immunocompetent patients. There were more RSV infections in the second year of our study. This confirms the known 2-year periodicity of RSV epidemics [8, 14]. In contrast, the dynamics of influenza epidemics are less predictable and onset as well as magnitude may vary in year to year comparisons [15, 23, 25].

Influenza infections contributed significantly to hospitalisations of children with respiratory symptoms in this investigation. Excluding patients with more than one infectious agent, mean hospitalisation rates were (per

Table 2 Comparative clinical findings in 175 patients hospitalised with RSV, influenza A or influenza B virus infection

	RSV ($n=119$) [a] Positive (%)	Influenza A ($n=42$) Positive (%)	Influenza B ($n=14$) Positive (%)	*P*
Major clinical diagnoses				
Upper respiratory tract illness	10 (8)	24 (57)	7 (50)	<0.001
Croup	0 (0)	2 (5)	1 (7)	<0.05
Bronchitis	21 (18)	3 (7)	3 (21)	0.22
Bronchiolitis/obstructive bronchitis	65 (55)	4 (10)	0 (0)	<0.001
Pneumonia	22 (18)	9 (21)	1 (7)	0.9
Myositis	0 (0)	0 (0)	2 (14)	<0.05
Signs, symptoms and complications				
Cough	98 (82)	32 (76)	8 (57)	0.09
Rhinorrhoea	81 (68)	19 (45)	6 (43)	<0.005
Pharyngitis	58 (49)	17 (41)	7 (50)	0.47
Fever (≥38°C)	68 (57)	38 (91)	12 (86)	<0.001
High fever (≥39°C)	34 (29)	30 (71)	7 (50)	<0.001
Dyspnoea	67 (56)	5 (12)	0 (0)	<0.001
Otitis media	29 (24)	11 (26)	1 (7)	0.66
Feeding difficulties/loss of appetite	79 (66)	21 (50)	4 (29)	<0.01
Vomiting	45 (38)	22 (52)	5 (36)	0.19
Diarrhoea	14 (12)	11 (26)	2 (14)	0.051
Febrile convulsions	2 (2)	9 (21)	2 (14)	<0.001
Treatment				
Oxygen administration	69 (58)	7 (17)	0 (0)	<0.001
Intensive care	10 (8)	2 (5)	0 (0)	0.24
Antibiotics	33 (28)	12 (29)	5 (33)	0.72

[a]One patient with RSV infection presented only with fever and feeding difficulties

Table 3 Comorbidity in patients with RSV and influenza A and B virus infections

Underlying conditions	Virus		
	RSV ($n=119$) Positive (%)	Influenza type A ($n=42$) Positive (%)	Influenza type B ($n=14$) Positive (%)
Prematurity	17 (14)	5 (12)	1 (7)
Chronic lung disease	5 (4)	1 (2)	1 (7)
Cardiovascular disease	4 (3)	0 (0)	0 (0)
Atopic eczema	3 (3)	2 (5)	1 (7)
CNS abnormalities	3 (3)	1 (2)	1 (7)
Others	3 (3)	3 (7)	0(0)
Any[a]	33 (28)	11 (26)	4 (29)

[a]Some patients had more than one underlying condition

100,000 and year) 39.5 and 141 for children <6 years of age and all children, respectively. These rates are in the range of a similar study performed in Germany, a country with comparable population characteristics [23]. It should be noted, however, that these rates probably are an underestimation of the true rates, because diagnostic tests had not been applied in all our patients.

High, unexplained fever and febrile convulsions, frequently associated with abrupt onset of high fever, were the major reasons for hospitalisation of those children. Similarly, febrile convulsions had occurred in 16% of children hospitalised with influenza in a Finnish study [20]. Most of our patients with influenza had symptoms of upper respiratory tract infections and establishing a diagnosis of influenza was helpful for their medical management. Accordingly, median duration of hospitalisation was short.

In comparison, children with RSV infections had a higher rate of lower respiratory tract symptoms and longer hospital stays, mainly because oxygen supplementation was required. The age distribution of patients with RSV infections (mainly infants) was markedly different from that of patients with influenza, most of whom were pre-school (influenza A) or school age (influenza B) children. A possible explanation for this difference may be that passively acquired maternal antibodies do provide some protection against influenza [21] but apparently not against RSV [5]. This is in accordance with previous findings from European studies [23, 25], whereas observations in the United States found highest rates for influenza hospitalisation for children in the first 2 years of life [17, 18]. We do not have a ready explanation for this geographic discrepancy.

Most of our patients with influenza were primarily healthy children. Although this finding is not new [20, 22], it indicates that the overall impact of the current immunisation strategy, which aims at patients with pre-existing chronic diseases, is limited. Moreover, the significant number of influenza patients with underlying diseases indicates that compliance with this strategy is suboptimal. More efforts are needed to improve this. If the goal was to prevent serious manifestations of influenza in all children, a general immunisation programme would be necessary. This strategy has recently been recommended by the "US Advisory Committee on

Immunization Practices'' for healthy 6–23-month-old children [3]. However, it is doubtful whether such a recommendation would be acceptable in Europe today.

Our study has some limitations. First, of 653 patients admitted to the hospital with respiratory symptoms, only 422 received diagnostic tests to detect RSV or influenza A/B infection. Therefore, it is likely that further cases among hospitalised patients remained undiagnosed. However, we do not believe that this has introduced a significant bias in our observational study since lack of diagnostic procedures appeared to be associated with individual physicians and not with the patient's presenting symptoms (data not shown). Further, sensitivity and specificity of RAT for RSV have been shown to be suboptimal [1]. Here, in children showing repeatedly positive RAT results, sensitivity and specificity when compared to RT-PCR was only 66% and 63%, respectively. When only children with positive PCR results were considered in our investigation, the rate of positive specimens decreased from 30% to 23%. Second, this study was limited to hospitalised patients and therefore does not allow any conclusions to be drawn concerning the whole spectrum of influenza disease.

Our results show, that influenza A or B, like RSV, infections are a major cause of hospitalisation in the paediatric population during winter seasons and investigations to better characterize the spectrum of serious complications of influenza in children are in progress. Based on such results, current immunisation recommendations—which primarily aim at protection of high risk patients—should be re-evaluated.

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