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Short Communication

Association between respiratory and herpes viruses on pulmonary exacerbations in cystic fibrosis patients

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Abstract

Respiratory viruses discovered in the 21st century and human herpes viruses ($N=13$) were seldom (4/50) detected in our cystic fibrosis patients although exacerbation frequency ($7.75 \pm 2.9/a$ versus $4.45 \pm 2.1/a$; $p=0.03$) and colonization with *Aspergillus fumigatus* (RR: 2.6; CI95: 1.8–3.7), *Pseudomonas aeruginosa* (RR: 1.84; CI95: 1.4–2.4), and *Staphylococcus aureus* (RR: 1.5; CI95: 1.2–1.9) including MRSA (RR: 4.6; CI95: 1.3–16.6) were associated with virus positivity. Further studies should clarify whether this finding reflects non-specific colonization (human Bocavirus) or reactivation (Epstein-Barr virus) or rather an acceleration of lung tissue inflammation.

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1. Background

Respiratory infections caused by common respiratory viruses are associated with an increase in morbidity in patients with cystic fibrosis (CF) [1–3]. The role of novel respiratory viruses (RVs) and human herpes viruses (HHVs) for acute pulmonary exacerbations in CF patients is currently unknown.

2. Methods

This prospective study investigated the role of eight novel RVs and five HHVs in patients with CF. Detailed patients' characteristics, clinical disease patterns, as well as pulmonary bacterial and fungal colonization patterns in the CF patients were included in order to conduct a risk factor analysis.

Respiratory specimens (sputum) consecutively sampled at the University Hospital Aachen from 07/07 to 06/08 of 50 CF patients were analyzed by nucleic acid amplification technologies (PCR; RT-PCR) for the presence of 13 viruses (human Cytomegalovirus, Epstein-Barr virus (EBV), *Herpes simplex virus* 1+2, *Varizella zoster virus*, human bocavirus (HBoV), human coronaviruses (229E, OC43, HKU1, NL63), human metapneumovirus, and human polyomaviruses (KIPyV, WUPyV)). Specimens were obtained routinely (2/3) and during exacerbation (1/3). For a summary of the key characteristics of the CF patients, see Table 1.

Clinical and microbial colonization data of the patients were analyzed statistically using the Mann–Whitney U test; for associations the risk ratios (RR) including 95% confidence intervals were given.

3. Results

HBoV DNA was detected in 1 patient (2%) and EBV DNA in 3 patients (6%) resulting in a positivity rate of 8%. Viral loads were 1.5×10^2 genome equivalents (geq)/ml for HBoV and

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Table 1
Characteristics of the CF patients (N=50).

Parameter	Mean±SD (range)
Age (years)	25±12 (1–67)
Height (m)	1.68±0.1 (1.18–1.88)
Weight (kg)	60±16 (20–140)
BMI ^a	21.3±5.5 (14.4–52.1)
Shwachman Score	60±13 (40–75)
FEV-1 ^b (l) ^c	2.1±1.0 (0.47–4.20)
Comorbidity	
	Frequency (%)
O ₂ inhalation therapy	13/50 (26)
ABPA ^d	6/50 (12)
DIOS ^e	6/50 (12)
Pancreatic insufficiency (exocrine)	46/50 (92)
Biliary cirrhosis	4/50 (8)
OLT ^f	2/50 (4)
Diabetes mellitus	14/50 (28)
Diabetes insipidus	5/50 (10)
Mutations	
	Frequency (%)
dF508/dF508	20/50 (40)
dF508/R553X	2/50 (4)
dF508/not dF508, not R553X	7/50 (14)
dF508/not —determined	9/50 (18)
R553X/R553X	2/50 (4)
R553X/not dF508, not R553X	1/50 (2)
Others	2/50 (4)
Not determined	7/50 (14)

^a BMI: body mass index.

^b FEV-1: forced expiratory volume.

^c Data available only for 49 patients.

^d ABPA: allergic bronchopulmonary aspergillosis.

^e DIOS: distal intestinal obstructive syndrome.

^f OLT^f: orthotopic liver transplantation.

ranged from 1×10^3 geq/ml to 9×10^4 geq/ml for EBV. Interestingly, patients tested positive for viral DNA had suffered significantly more pulmonary exacerbations during the preceding year (7.75, SD: 2.06 vs. 4.45, SD: 2.92; $p=0.03$). Furthermore, all four virus-positive patients were colonized with *Aspergillus fumigatus* (RR: 2.56; CI95: 1.78–3.66); *Pseudomonas aeruginosa* (RR: 1.84; CI95: 1.41–2.40), and *Staphylococcus aureus* (RR: 1.53; CI95: 1.24–1.89) and these patients were significantly more often positive for MRSA (RR: 4.6; CI95: 1.28–16.59). For further clinical and microbial data of the CF patients, see Table 2.

4. Conclusions

Common respiratory viruses like respiratory syncytial virus (RSV), influenza viruses, and adenoviruses have been shown to increase morbidity in CF patients [1]. Although CF patients do not contract respiratory infections any more frequently than patients without CF, when they do, these infections seem to have a greater impact on morbidity of CF patients compared to patients without CF [1,4,5]. During the last decade, HHVs were increasingly recognized as respiratory pathogens and since then several novel RVs have been discovered [6]. However, whether these novel viruses play a pathogenic or passenger role in regards to respiratory diseases is still an ongoing debate [7].

Table 2
Clinical and microbial data of the CF patients.

	Virus-negative patients (n=46)	Virus-positive patients (n=4)	Associations/differences
Age (range)	25±12 (1–68)	19±8 (11–29)	ns ^a
Gender (m:f)	25:21	3:1	ns ^a
Exacerbations ^b /year (SD)	4.45 (±2.9)	7.75 (±2.1)	$p=0.03^a$
Colonization (%) with			
<i>S. aureus</i>	30 (65%)	4 (100%)	RR ^c : 1.53 (CI95: 1.24–1.89)
MRSA	5 (11%)	2 (50%)	RR ^c : 4.60 (CI95: 1.28–16.59)
<i>Ps. aeruginosa</i>	25 (54%)	4 (100%)	RR ^c : 1.84 (CI95: 1.41–2.40)
Enterobacteriaceae	15 (33%)	0 (0%)	ns ^c
<i>H. influenzae</i>	9 (20%)	0 (0%)	ns ^c
Alcaligenaceae	9 (20%)	0 (0%)	ns ^c
<i>S. maltophilia</i>	7 (15%)	0 (0%)	ns ^c
<i>Aspergillus fumigatus</i>	18 (39%)	4 (100%)	RR ^c : 2.56 (CI95: 1.78–3.66)
Shwachman Score	60 (±13)	61 (±13)	ns ^a
BMI ^d	21 (5.6)	21 (3.5)	ns ^a
Mutation: not dF508/dF508	19 (41%)	3 (75%)	ns ^c
Mutation: not dF508/... or R553X/...	1 (2%)	1 (25%)	ns ^c
ABPA ^e	5 (11%)	1 (25%)	ns ^c
D. mellitus and/or D. insipidus	13/5 (28/11%)	0/0 (0/0%)	ns ^c
Pancreatic insufficiency	42 (91%)	4 (100%)	ns ^c

^a Mann–Whitney *U* test.

^b Exacerbation (definition): consultation of the physician because of acute pulmonary deterioration suggestive for infection.

^c RR: risk ratio; CI95: 95% confidence interval.

^d BMI: body mass index.

^e ABPA: allergic bronchopulmonary aspergillosis.

Patients only tested positive for 2 of the 13 viruses (HBoV = 1, EBV = 3). This detection rate of 8% is known to be similarly low in non-CF patients indicating that the 13 viruses tested for do not frequently account for most pulmonary exacerbations in patients with CF [6,8]. Retrospective studies report that HBoV is most prevalent in infants up to the age of 2 years [7]. It should also be borne in mind that most of respiratory virus infections occur during childhood and therefore, age may be the most important risk factor [6,9]. Thus, as our cohort consisted of mostly adults, we cannot exclude the possibility that age effects may have biased our results. Previous investigations demonstrated a higher frequency of pulmonary exacerbations for common respiratory viruses like RSV [1,4,10]. In line with these results, we found that the pulmonary exacerbation frequency was significantly associated with virus positivity in this study. However, we did not detect any deterioration of the Shwachman Score or a decline of FEV1 as shown for common respiratory viruses [1,4,10,11]. Moreover, our results indicate an association of virus positivity with colonization by *A. fumigatus*, *P. aeruginosa*, and *Staphylococcus* species (including MRSA). For other well-known respiratory viruses, an association with several of the same bacterial pathogens has been previously suggested [1,11,12]. A limitation is the small number of CF patients participating in our study. Further studies

should clarify whether our findings reflect a non-specific colonization (HBoV) or reactivation (EBV) in an otherwise severely infected organ or if these viral infections worsen lung tissue inflammation and thus accelerate the progression of lung disease in CF.

Results were partly presented at the 61st Annual Meeting of the German Society of Microbiology and Hygiene (DGHM) in Göttingen, Germany (20–23 September 2009)[13].

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