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Scientific Letter

Possible Involvement of Infection with Human Rhinoviruses in Children with Kawasaki Disease

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To the editor.

Kawasaki disease (KD) is a common childhood disease that primarily affects small- and medium-sized arteries, particularly the coronary arteries, causing severe cardiovascular disease. It is generally accepted that KD is an autoimmune disorder activated by various microbial agents.[1-4]

Previous research found that roughly one-third of children with KD developed respiratory symptoms.[5,6] Before confirming the diagnosis of KD, febrile children with respiratory symptoms undergo laboratory testing to identify respiratory viruses.[5,6] Human rhinoviruses (HRV), a common cause of the common cold, can lead to various clinical manifestations beyond the typical upper respiratory symptoms, ranging from exacerbations of underlying lung diseases to extrapulmonary complications.[7] There have been isolated case reports tentatively suggesting a potential association between HRV infections and KD in children.[8,9] However, convincing evidence from well-designed epidemiological studies is still lacking, and the mechanisms behind this putative association remain elusive.

This study aimed to investigate the possible role of HRV infection in the development of KD. Children with KD who tested negative for respiratory viruses and those who tested positive for other respiratory viruses served as controls. By analyzing and comparing the three groups' demographic, clinical, and laboratory characteristics, this study attempted to gain further insight into the potential contribution of HRV infection to the pathogenesis of KD.

Methods.

Patient selection. According to the American Heart Association, KD is distinguished by a 5-day fever and at least four of the five primary clinical characteristics of KD.[9] Between January 2022 and December 2022, children hospitalized with KD who tested positive for HRV were enrolled as the study subjects. At the same time, children with KD who tested positive for other respiratory viruses and those with negative respiratory virus tests were enrolled as control groups for comparison.

Laboratory tests. In addition to Mycoplasma pneumoniae and Chlamydia, a panel of respiratory viruses, including Flu A (H1N1 and H3N2) and B, respiratory syncytial virus (RSV), human parainfluenza virus (HPIV), HRV, human metapneumovirus (HMPV), human coronavirus (HCoV: NL63, OC43, 229E, and HKU1), human adenovirus (HAdV), and human bocavirus (HBoV)were detected in these specimens using commercial polymerase chain reaction (PCR) – capillary electrophoresis kits (Ningbo Haiers Gene Technology Co., Ltd., China).

Exclusion criteria. The exclusion criteria included the following: (1) patients with potential chronic diseases (e.g., congenital anomalies; genetic disorders; immunodeficiency; and autoimmune, cardiovascular, endocrinologic, hematological, hepatobiliary tract, or respiratory diseases), (2) coinfection with bacteria or other pathogens, and (3) patients with insufficient clinical data.

Statistical analyses. The statistical analyses were performed using SPSS ver. 21.0 software (SPSS, Inc., Chicago, IL, USA). Chi-square or Fisher's exact tests were used to compare group frequency distributions. Normally distributed continuous data are presented as mean ± standard deviation. The mean values between groups were compared using the independent sample *t*-test. A P value of <0.05 was considered statistically significant.

Results.

Demographic information and basic clinical features of the cases. A total of 21 children with KD tested positive for respiratory viruses, including 11 who were positive

Table 1. The baseline characteristics of KD patients with respiratory viral infection.

No.	Gender	Age	Chief complaint or Physical examination	Admission diagnosis	Discharge diagnosis	Hospital stays (days)	Virus detected
1	Female	1y	Fever, rash, cough	KD, URIs	KD, URIs	15	HRV
2	Female	5m	Fever, cough	KD, pneumonia	KD, pneumonia	7	HRV
3	Male	11m	Fever, rash	KD, URIs	KD, URIs	5	HRV
4	Male	3y	Fever, rash, cough	KD	KD, tracheitis	8	HRV
5	Male	6m	Fever	URIs	KD, pneumonia	10	HRV
6	Female	3y	Fever, sleepiness	KD, pneumonia	Incomplete KD, pneumonia	12	HRV
7	Female	6y	Fever, rash	URIs	Incomplete KD, URIs	9	HRV
8	Female	2y	Fever, conjunctival congestion	URIs	KD, pneumonia	6	HRV
9	Male	1y	Fever, rash, cough	Tracheitis	KD, pneumonia	8	HRV
10	Male	2y	Fever, rash	KD, URIs	KD, URIs	7	HRV
11	Male	5y	Fever, abdominalgia, dyspnea	KD, pneumonia	KD, pneumonia	13	HRV
12	Male	3y	Fever, cough	URIs	KD, bronchitis	8	HCoV
13	Male	1y	Fever, rash	Trachitis, laryngitis	KD,trachitis, laryngitis	7	HCoV
14	Male	3y	Fever, rash	URIs	KD, URIs	11	HCoV
15	Male	1y	Fever, rash	KD, URIs	KD, URIs	12	HCoV
16	Male	5y	Fever	URIs	KD, pneumonia, thrombocytopenia	8	HCoV
17	Female	1y	Fever	URIs	KD, URIs	6	RSV
18	Male	1y	Fever, rash	URIs	KD, bronchitis	6	RSV
19	Female	1y	Fever	Thrombocytopenia	Incomplete KD, pneumonia, thrombocytopenia	7	HBoV
20	Female	8m	Fever, rash, cough	Tracheitis	Incomplete KD, tracheitis	10	HMPV
21	Female	7y	Fever	URIs	Incomplete KD, URIs	8	HAdV

for HRV and 10 who were positive for other respiratory viruses: 5 for HCoV, 1 for HBoV, 2 for RSV, 1 for HAdV, and 1 for HMPV. Of the 11 KD children with HRV infection, 4 (36.4%) were admitted with respiratory tract infection, and 6 (54.5%) were admitted with KD accompanied by respiratory tract infection. In the discharge diagnosis, four cases (36.4%) had upper respiratory tract infections (URIs), one (9.1%) had tracheitis, and six (54.5%) had pneumonia. The demographic information and basic clinical features of the cases are listed in **Table 1**.

Comparison of the clinical characteristics between KD patients with HRV infection and with other respiratory viral infections. The clinical characteristics between KD patients with HRV infection and other respiratory viral infections are listed in **Table 2**. Patients with HRV infection had the highest rate of clinical presentation as oral mucosal changes ($p = 0.035$) and cervical lymphadenopathy ($p = 0.008$).

Comparison of the clinical characteristics between KD patients with and without respiratory viral infection. The results presented in **Table 3** indicated that the rate of conjunctival injection was lower in the KD group with HRV infection than in the group of KD patients who tested negative for respiratory viruses ($p = 0.028$). The KD group with other respiratory viral infections had significantly lower conjunctival injection ($p = 0.006$), oral mucosal changes ($p < 0.001$), extremity changes ($p = 0.008$), cervical lymphadenopathy ($p = 0.009$), and white blood cell count ($p = 0.043$). In contrast, coronary artery lesions ($p = 0.002$) were substantially elevated.

Discussion. Of the 11 KD children with HRV infection, 36.4% had a respiratory tract infection at the time of admission, and 54.5% had KD and a respiratory tract infection. While this study could not conclusively establish the sequence of events leading from HRV respiratory infection to KD onset, the association suggests that HRV infection likely contributes to the risk of developing KD, at least in some children. HRV infection may act as a co-factor that, in concert with other genetic and environmental factors, plays a role in the pathogenesis of KD in susceptible individuals. According to recent studies, one-half of patients with KD were positive for a respiratory virus by PCR, and a large proportion of patients with KD presented with concurrent respiratory symptoms.[5,11,12]

We found that children with HRV-associated KD

Table 2. Comparison of the clinical characteristics between KD patients with HRV infection and other respiratory virus infections.

	Clinical Information		KD with HRV infection (n=11)	KD with other respiratory virus infections (n=10)	*p*
Demography	Sex, n (%) male		6(54.5)	6(60.0)	1.000
	Age (year)	<1	3(27.3)	1(10.0)	0.850
		1-2	4(36.4)	5(50.0)	
		3-5	3(27.3)	3(30.0)	
		≥6	1(9.1)	1(10.0)	
Clinical presentation	Conjunctival injection, n (%)		5(45.5)	3(30.0)	0.659
	Oral mucosal changes, n (%)		5(45.5)	0(0.0)	0.035
	Changes of the extremities, n (%)		4(36.4)	1(10.0)	0.311
	Polymorphous rash, n (%)		6(54.5)	5(50.0)	1.000
	Cervical lymphadenopathy, n (%)		10(90.9)	3(30.0)	0.008
	Coronary artery lesions, n (%)		2(18.2)	4(40.0)	0.361
	Cough, n (%)		10(90.9)	9(90.0)	1.000
	Wheezing, n (%)		2(18.2)	0(0.0)	0.476
	Rales, n (%)		4(36.4)	1(10.0)	0.311
Diagnosis	Complete KD		8(72.7)	7(70.0)	1.000
	Incomplete KD		3(27.3)	3(30.0)	
	Pneumonia		6(54.5)	2(20.0)	0.216
	Tracheitis/bronchitis		1(9.1)	4(40.0)	
	URIs		4(36.4)	4(40.0)	
Treatment	PICU admission, n (%)		1(9.1)	0(0.00)	1.000
	Hospital stays (days)		9.09±3.113	8.30±2.058	0.505
Laboratory examination on admission	WBC count, × 10^9/L		11.93±3.221	10.55±3.331	0.344
	Neutrophils (%)		66.29±14.081	60.17±18.629	0.403
	Lymphocytes (%)		24.09±10.289	28.52±15.428	0.444
	PLT count, × 10^9/L		259.45±108.995	263.20±173.640	0.953
	Hb , g/L		108.64±13.508	113.20±11.830	0.422
	ALT, U/L		90.01±76.646	68.73±104.908	0.599
	AST, U/L		57.21±40.802	110.51±133.669	0.252
	CK-MB, U/L		21.02±7.440	21.33±8.235	0.930
	LDH, U/L		273.45±53.999	349.67±136.721	0.146

had a much higher incidence of oral mucosal changes and cervical lymphadenopathy than children with KD related to other viruses. Even though numerous respiratory viruses display similar symptoms, they can have contrasted clinical manifestations.[13,14] In other words, while various respiratory viruses appear to trigger a generally comparable syndrome known as KD with overlapping symptoms and signs, differences remain in the precise clinical manifestations between instances linked to separate viruses. The observed clinical differences could stem from intrinsic HRV tropism for upper respiratory tissues or divergent immune responses provoked by HRV during KD pathogenesis compared to mechanisms of other respiratory viruses triggering KD.

In this study, children with Kawasaki disease linked to respiratory virus infection (virus-positive KD group) exhibited significantly lower rates of conjunctival injection, oral mucosal changes, extremity changes, and swollen lymph nodes than children without detectable respiratory virus (virus-negative KD group). However, coronary artery lesions were significantly more common in the virus-positive KD group, particularly in the subset of children with HCoV (3 cases) or HMPV (1 case) detected. These results suggest that:

1. Respiratory virus-associated KD may represent a clinically distinct subset with a different symptom profile due to distinct disease mechanisms.
2. HCoV and HMPV, in particular, may be linked to a very severe course of KD with a higher propensity for coronary lesions, potentially due to differences in viral tropism or host response. These viruses could more readily infect tissues involved in coronary damage or elicit an immune reaction promoting vasculitis. Genetics may also play a role in disease severity.
3. Larger scale studies are still needed to validate links

Table 3. Comparison of the clinical characteristics between KD patients with and without respiratory viral infection.

	Clinical Information		KD without respiratory viruses infection (n=82)	KD with HRV infection (n=11)	*p*	KD with other respiratory virus infection (n=10)	*p*
Demography	Sex, n (%) male		51(62.2)	6(54.5)	0.625	6(60.0)	1.000
	Age (year)	<1	17(20.7)	3(27.3)	0.829	1(10.0)	0.807
		1-2	33(40.2)	4(36.4)		5(50.0)	
		3-5	27(32.9)	3(27.3)		3(30.0)	
		≥6	5(6.1)	1(9.1)		1(10.0)	
Clinical presentation	Conjunctival injection, n (%)		63(76.8)	5(45.5)	0.028	3(30.0)	0.006
	Oral mucosal changes, n (%)		60(73.2)	5(45.5)	0.06	0(0.0)	<0.001
	Changes of the extremities, n (%)		49(59.8)	4(36.4)	0.251	1(10.0)	0.008
	Polymorphous rash, n (%)		62(75.6)	6(54.5)	0.139	5(50.0)	0.086
	Cervical lymphadenopathy, n (%)		62(75.6)	10(90.9)	0.450	3(30.0)	0.009
	Coronary artery lesions, n (%)		4(4.9)	2(18.2)	0.302	4(40.0)	0.002
Diagnosis	Complete KD		71(86.6)	8(72.7)	0.448	7(70.0)	0.362
	Incomplete KD		11(13.4)	3(27.3)		3(30.0)	
Treatment	PICU admission, n (%)		5(6.1)	1(9.1)	1.000	0(0.0)	1.000
	Hospital stays (days)		7.90±2.57	9.09±3.113	0.164	8.30±2.058	0.639
Laboratory examination on admission	WBC count, × 10^9/L		14.19±5.47	11.93±3.221	0.186	10.55±3.331	0.043
	Neutrophils (%)		67.32±15.49	66.29±14.081	0.835	60.17±18.629	0.181
	Lymphocytes (%)		23.79±13.47	24.09±10.289	0.943	28.52±15.428	0.305
	PLT count, × 10^9/L		331.09±119.46	259.45±108.995	0.063	263.20±173.640	0.111
	Hb, g/L		109.01±10.10	108.64±13.508	0.912	113.20±11.830	0.227
	ALT, U/L		69.18±126.97	90.01±76.646	0.598	68.73±104.908	0.991
	AST, U/L		71.19±145.59	57.21±40.802	0.753	110.51±133.669	0.419
	CK-MB, U/L		30.22±21.63	21.02±7.440	0.167	21.33±8.235	0.203
	LDH, U/L		344.19±126.68	273.45±53.999	0.072	349.67±136.721	0.903

between individual respiratory viruses and KD severity, as this study has limited power due to small sample sizes, especially for HMPV (1 case).

4. Longer follow-up is also needed to determine longer-term outcomes, as the degree of initial coronary changes does not necessarily directly correlate with the need for intervention or resolution of disease. Some cases with less initial coronary damage could progress over time, while others remain stable. Furthermore, studies have indicated that IVIG can stave off coronary artery abnormalities but has limited efficacy when treating existing coronary damage.[15] All patients with coronary artery anomalies in our study, both in the case and control groups, were given IVIG within two days of being diagnosed with KD. Only one case with concurrent HRV infection showed no response to IVIG treatment. As a result, this element has little impact on our conclusions.

Our study also has some limitations. First, this is a retrospective study, and not all KD patients underwent respiratory pathogen testing, so some potential positive cases may have been missed. Second, the number of positive cases is relatively small, which may lead to statistical bias. Finally, pathogen testing only involved the detection of common respiratory pathogens. In the control group, some infected KD cases may have had potential infections from non-respiratory viruses. Further large-scale, multi-center prospective studies are warranted to validate and extend these findings.

Conclusions. In this study, we reported 11 HRV-associated KD and 10 cases of other respiratory virus-associated KD cases. We compared the parameters between these two groups and respiratory virus-negative KD cases. Larger sample sizes are needed to confirm these differences and elucidate whether KD cases triggered by different infectious agents have distinct mechanisms of pathogenesis, which will facilitate more personalized diagnosis and treatment approaches tailored to the specific infectious trigger.

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Competing interests: The authors declare no conflict of Interest.

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