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Cardiac Complications Caused by Respiratory Syncytial Virus Infection: Questionnaire Survey and a Literature Review

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Abstract

We investigated 22 cases of patients with myocarditis during respiratory syncytial virus (RSV) infection by a questionnaire survey, and performed a literature search to clarify their characteristics. The age distribution was divided into 2 groups, that is, 1 group comprised of patients younger than 4-years old and the other comprised patients older than 15 years. ECG demonstrated disturbance of the conduction system (AV block) in 7 out of 18 patients (38.8%), myocardial damage (ST-T change) in 9 out of 18 patients (50.0%), and tachycardia in 3 out of 18 patients (16.6%). Echocardiography displayed a robust decrease in left-heart function in 12 out of 14 patients. The outcome was 2 deaths, 1 pacemaker placement, 4 patients with mild sequel. Our data suggest that RSV myocarditis caused by RSV infection can be divided into 3 different pathophysiologies, characterized by disturbance of the conduction system, myocardial damage, and increase of autonomy.

Keywords

SIDS, AV block, myocardial damage, tachycardia, NT-pro BNP

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Respiratory syncytial virus (RSV) is a worldwide common cause of childhood respiratory infection that can result in death. A report from Taiwan demonstrated that between 2004 and 2007, the annual hospitalization incidence of patients with RSV infection was 1077 and 232 per 100 000 children-years in children under 6 months and under 5 years of age, respectively.[1] Fatality during hospitalization for severe RSV infection of the lower respiratory-tract occurs commonly among children especially at higher risk. A systematic review reported that the weighted mean case-fatality rate was 1.2% among preterm infants; 5.2% among children with congenital heart diseases; and 4.1% among children with broncho**pulmonary** dysplasia. However, the weighted mean case-fatality estimates among children not at high risk was 0.2%.[2] An investigation in Japan reported that the reasons for RSV hospitalization in 359 children without underlying diseases were severe bronchiolitis (81.6%), RSV encephalitis (5.3%), near-miss sudden infant death syndrome (SIDS) (3.1%), RSV myocarditis (1.4%), SIDS (0.3%), and others (8.4%).[3]

Viral infections are considered to be the most common etiology of myocarditis.[4] RSV myocarditis has been reported as a cause of viral myocarditis in both the pediatric and adult populations. However, the details of RSV-associated myocarditis have not been clarified to date. Sudden death and similar conditions occur by several pathophysiologies, such as respiratory distress,

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Table 1. The literature review and the patients collected by questionnaire.

Patient number	Age at onset	Sex	Ethnicity/country	Underlying diseases	Symptoms	Heart rate	Respiratory rate	Chest X-ray	WBC (μL)
1	1 month	M	African American		Upper respiratory symptoms, decreased oral intake, nonbilious vomiting	Bradycardia		Hyperinflation with perihilar atelectasis	Increased ESR
2	1 month	M	Japanese		Cough, rhinorrhea, decreased feeding	215	60	Normal	7400
3	3 months	F	Hispanic		Persistent crying, difficulty breathing, diminished appetite	200 (gallop)	84 (tachypnea)	Enlarged heart shadow	
4	3 months	M	Hispanic		Fever, cyanosis	300		Cardiomegaly, diffuse patchy lung infiltrate	
5	5 months	F	Japanese	Mild TR	Fever, cough, rhinorrhea, tachypnea			Abnormal (details unknown)	17 700
6	7 months	F	Hispanic	None	Rhinorrhea, fever, wheezing	200-220	80-90		18 800
7	8 months	F	Japanese	None	Cough, rhinorrhea, decreased feeding				
8	9 months	F	Japanese		Fever, cough, rhinorrhea, tachypnea				22 200
9	10 months	M	Greek	None	Low grade fever, cough	70	Sat 90%		
10	Infant	M	Japanese		Unknown				
11	1 year	F	Japanese	Kawasaki disease without sequela	Fever, cough			Infiltration, effusion	9400
12	1 year	M	Japanese		Mild stridor and sudden death				
13	2 years	F	Japanese		Common cold symptoms	188			
14	3 years	F	Japanese	Low birth weight (2150 g)	Rhinorrhea, tachypnea, dyspnea		Sat 80%	Effusion, cardiac enlargement	17 000
15	3 years	M	Australia		Loose cough, vomiting, stridor, fever				Increased ESR
16	3 years	Unknown	None((unknown?))	RS infection at 3 months of age	Slow heart rate	30 (bradycardia)	None		
17	4 years	F	Japanese	ALL	High fever, tachypnea, tachycardia	180	38	Mild perihilar infiltration	322 (neutrophils)
18	15 years	M	USA		Syncopy 2 weeks after cough and fever	30		Cardiomegaly, prominence of hilar vessels	8700
19	23 years	M	USA		Dyspnea and chest pain	110		Cardiomegaly, vascular congestion	13 200
20	40 years	M	African American		Fever, chills, dyspnea	130	30		
21	58 years	M	Japanese		Vertigo and fever 2 weeks after common cold symptoms				9000
22	59 years	F	Japanese		Fever and dyspnea 4 weeks after common cold symptoms				9300

Vacant boxes are unwritten information in detail.

CRP (mg/dL)	CPK (U/L)	BNP (pg/mL)	Troponin-I	Echocardiography	ECG	Medication	Response	Others	Report
			Not tested	EF 33%	Ventricular tachyhcardia, PVCs, ST segment elevation	Lidocaine, decadron, inderal	Good		Huang et al[5]
0.24			0.15	WNL	2:1 conduction AF	Gamma-globulin	Good		Araki et al[6]
				EF 21%	Narrow QRS →AF	Lidocaine, amirinone, digoxin, ECMO	Good		Thomas et al[7]
				EF 16%	Supraventricular tachycardia	ATP, dopamine, dobutamine, lidocaine, HFO	Motor delay		Thomas et al[7]
	1100	46.4	Negative	EF 18%, MR	ST change	Catecolamine	Mild decreasing in cardiac function	Rapid test	Questionnaire
			0.518	EF 38%	Sinus tachycardia	Furosemide, incubation, milrinone	Good		Menchise[8]
				EF decreased		Catecolamine, PDE inhibitor	Died	Myocarditis confirmed by autopsy	Questionnaire
	373		Increased	Enlargement of left ventricle, EF decreased	ST change	Not stated		Rapid test	Questionnaire
			Not increased	Normal, PR	Complete heart block	IVIG	Good		Karatza et al[9]
							Died	Myocarditis confirmed by autopsy	Endo and colleagues[10]
	700	937	Negative	FS 29.6	AV block	Catecholamine, PDE blocker, HANP, pacing, ventilation	mild decreasing cardiac function	Rapid test	Questionnaire
							Died	Myocarditis confirmed by autopsy	Goto et al[11]
				EF decreased, ventricular wall thickening		VA-ECMO	Good		Mizuno et al[12]
	4441	2766	Increased	EF 9.2%, MR	T change	Catecolamine, PDE inhibitor	Mild decreasing cardiac function	Rapid test	Questionnaire
					Wenckebach AV block, ST elevation, flat T wave	None	Good		Menahem and Uren[13]
					Complete heart block				Menehem[14]
2.2			0.541	EF 27%, Tei 0.62	ST-T change V4-6	CHF, IVIG, mechanical ventilation	Good	Type B (serum RNA 1.4×10^8)	Miura et al[15]
	128				Complete AV block	Temporary pacemaker	Prolongation of PR interval	Serological diagnosis	Giles and Gohd[16]
				Enlargement of left and right ventricle, poor motion of left ventricular posterior wall	Nonspecific T change, left atrial enlargement, QRS complexes (left and right ventricle enlargement)	Digitalis, diuretics	Good	Serological diagnosis	Giles and Gohd[16]
2.2			1.01	EF 10–15%	T inversion V4-6	VA-ECMO	Good	Type A	Milas et al[17]
7+					Complete AV block	Pacemaker	Pacemaker	Serological diagnosis	Taira et al[18]
3+					PAC, PVC, sinus arrest	Diuretics	Heart failure	Serological diagnosis	Taira et al[18]

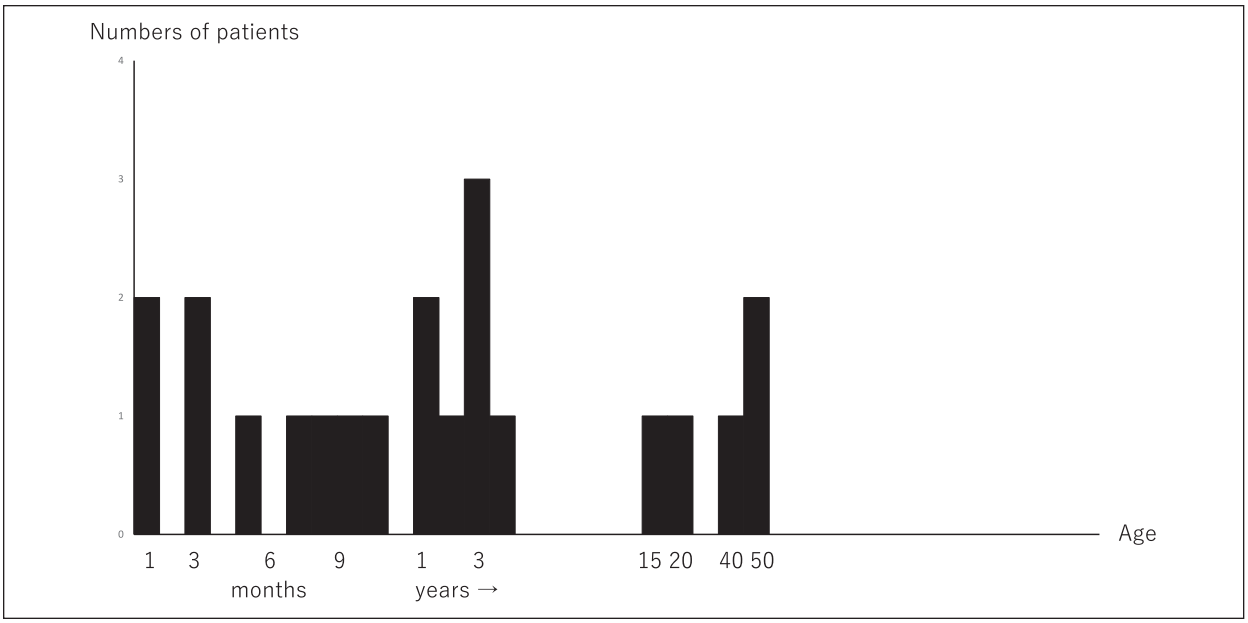

Figure 1. Age distribution of patients with RSV-associated myocarditis.

cardiac problems, and neurological diseases, which are often accompanied with RSV infection. In particular, cardiac manifestations, such as myocarditis, can readily cause fatality in children. In this study, we collected clinical records by questionnaire and reviewed the literature to know the actual situation and their pathophysiology of RSV-associated myocarditis.

Methods

The literature review and the patients collected by questionnaire which was conducted by us[3] are shown in Table 1. The literature review are questionnaire was conducted cases with arrhythmia and myocarditis during RSV infection. There were 22 patients (mean and S.D; 10.2 and 18.75 years) without congenital heart disease or serious pulmonary diseases, of which 2 were fatal. The 17 pediatric patients were aged from 1 month to 15 years (average: 2.1-years old), including 10 patients under 1-year old. The sex ratio was 10 boys and 11 girls (1 patient was unknown). Three of the twenty-two patients had underlying diseases (ALL, neonatal HSV infection, and mild Tricuspid regurgitation).

Results

The patients were divided into 2 groups by age, that is, 1 group comprised patients younger than 4-years old (16/21 patients: 76.2%) and the other comprised of patients older than 15 years. The latter group mostly developed myocarditis after 2 to 4 weeks after RS infection (Figure 1 and Table 1). Symptoms, excluding those of late-onset cases, were fever (7/13), convulsions (1/13), and cardiopulmonary arrest on arrival (0/13). Laboratory findings were as follows: white blood cell (WBC) count, 7400 to 22 200/μL; C-reactive protein, 0.07 to 3.09 mg/dL; and creatine kinase (CPK), 43 to 373 IU/L. White blood cell counts increased in 9 out of the 11 patients tested. Virus analysis in nasal aspiration was performed and 1 patient each was positive for RSV type B with RNA 1.6×10^9 and RSV type A by RT-LAMP (positive predictive value 94% and negative predictive value 94%).[19] ECG displayed disturbance of the conduction system (AV block) in 7 out of 18 patients (38.8%), myocardial damage (ST-T change) in 9 out of 18 patients (50.0%) including both 1 case, and tachycardia in 3 patients (16.6%). Echocardiography showed a substantial decrease in left-heart function in 12 out of 14 patients. Chest X-ray showed normal to mild perihilar infiltration, hyperinflation with perihilar atelectasis, including 2 patients with effusion. Five patients showed cardiomegaly. Supportive therapies, including pacemaker placement were provided. Intravenous immunoglobulin was administered to 4 out of 19 patients. Continuous blood purification (CHF) and extra-corporeal membrane oxygenation (ECMO) were performed in 3 out of 19 patients. The outcome was as follows: 2 fatal, 1 pacemaker placement, 4 patients with mild sequelae, and 1 patient with sequela of motor delay.

Autopsy showed sparse lymphocytes, mild perimyocytic fibrosis, and no cellular necrosis. This patient (number 2 in Table 1) had 1 day of nasal discharge, coughing, and wheezing. On the following day milk intake decreased and no urination was confirmed. She

Table 2. Classification of Cardiac Pathogenesis on RSV Infection by ECG.

	Type 1	Type 2	Type 3
ECG	Block pattern	ST-T change	Tachycardia
Main age	All age	All age	Mainly early infants
Ejection fraction (EF)	Normal	↓↓	↓
Progression	Rapid	Gradually	Relative rapid
Correlation of sudden death	High	Low	Low
Outcome	Seldom poor	Seldom poor	Almost good
Suspected pathology	Direct viral invasion	Myocardial damage	Increased autonomy

was admitted to hospital because of a positive RSV rapid test. On admission, depressed breathing, tachypnea, no fever, and cold limbs were observed. Chest examination demonstrated expiratory wheezing and decreased breathing sounds. Therefore, administration of neophyllin, and echocardiography was performed. The patient's ejection fraction was markedly decreased. Under the diagnosis of myocarditis, diuretics, catecholamine, and nitroglycerin were given. Bradycardia and cardiac arrest, as well as cardiopulmonary arrest occurred and death was confirmed without response after 5 hours of admission.

Discussion

Apnea and bradycardia are often associated with RSV infections.[20-22] Fetal and lethal arrhythmias, similar to bradyarrhythmia and supraventricular tachycardia owing to myocarditis have been reported to occur in patients with RSV infection.[5,7,14,23-25] Goto et al[11] found cell infiltration in the myocardium and conduction system on autopsy of a 1-year old boy with asthmatic bronchitis who died suddenly. A systematic review by Eisenhut et al[26] showed that extrapulmonary manifestations of RSV infection were cardiovascular failure with hypotension, and inotrope requirement associated with myocardial damage, as evident from increased cardiac troponin levels (35%-54% of ventilated infants), cardiac arrhythmias, such as supraventricular tachycardias and ventricular tachycardias, central apneas, focal and generalized seizures, focal neurological abnormalities, and hepatitis. From those data arrythmia assumed to be caused by invasion of RSV directly or reaction against heart failure by bloodstream infection. Rohwedder et al[27] investigated nasal washes and blood samples by using nested reverse transcription and polymerase chain reaction (RT-PCR) and found 6 out of 20 infected cases were positive for RSV-RNA in blood, and concluded that viremia may be a frequent occurrence in neonates and young children.

Myocarditis is defined as the inflammation of cardiac muscle causing myocellular damage leading to cardiac dysfunction and possibly heart failure. Viral infections are considered to be the most common etiology of myocarditis. RSV-associated myocarditis is considered to be a rare cause of viral myocarditis in both the pediatric and adult population. In 12 pediatric and 5 adult patients hospitalized for acute myocarditis, serum samples in the acute phase were positive for viral sequences in 7 (41%) of the 17 myocarditis patients using next-generation sequencing (NGS). Among these patients, RSV reads by NGS were detected in 1 patient.[28] Polymerase chain reaction (PCR) identified adenovirus as the most common virus from cardiac samples in the myocardium of children and adults with myocarditis and dilated cardiomyopathy (DCM). RSV was detected in only 1 out of 239 virus-positive patients.[29] In the investigation by Akhtar et al[30] PCR for the detection of DNA viruses (adenovirus, cytomegalovirus, herpes-simplex virus, and Epstein-Barr virus) and RNA viruses (enterovirus, RSV, and influenza) showed no RSV-positive patients with myocarditis.

On the other hand, previous studies have demonstrated the development of myocardial damage and hepatitis in children with severe RSV infection. Seven (20%) out of 35 ventilated infants with RSV bronchiolitis had an increased right ventricular Tei index indicating reduced right ventricular function. Cardiac troponin T level was increased in 14 patients (41%).[31] Esposito studied the frequency of heart involvement in infants with bronchiolitis associated with RSV infection in 69 healthy infants. They reported that sinoatrial blocks were identified in 26/34 RSV-positive patients and 1/35 RSV-negative patients (2.9%). They also found that the sinoatrial (SA) blocks were significantly more frequent in children with an RSV load of $\geq$100 000 copies/mL than in those with a lower viral load.[32]

From the results of ECG, RSV-associated myocarditis can be divided into 3 groups referencing Butta's report.[33] The first group is characterized by disturbance of the conduction system. The second group is characterized mainly by myocardial damage. The third group is characterized by excessive autonomy which are considered by tachycardia without severe heart failure (Table 2). The first group showed normal

images on echocardiography. Goto et al[11] found cell infiltration in the myocardium and conduction system in autopsy samples of a 1-year-old boy with asthmatic bronchitis who died suddenly, and suspected that the direct invasion of viruses causes serious arrhythmia. Therefore, the first group has a high risk for RSV infection.

We have encountered 3 patients with cardiopulmonary arrest caused by RSV infection (manuscript in submission). One patient, who survived after intensive care, showed arrhythmia and was positive for RSV in the cerebrospinal fluid. There have been many reports on the correlation between sudden death and RSV. Williams et al[34] investigated the presence of viruses in the respiratory tract of 763 patients who died of sudden infant death during a 9-year period, and showed that 3 out of the 385 (0.8%) patients were younger than 3 months of age and 25 out of the 378 patients (6.6%) were positive for RSV in 1984. Postmortem isolation of RSV from SIDS patients is more common than from non-SIDS infants.[35] A recently established sensitive assay that uses real-time PCR also showed similar results. In a study of 403 hospitalized children, sudden death occurred in 7 out of 15 infants who had acute respiratory infections, 6 of which were caused by RSV.[36] Parham et al[37] proposed that signs of viral infection are usually inconsequential in SIDS infants, because RSV infections are almost universal during infancy and infrequently lead to death, even in hospitalized patients. They concluded that RSV may be a precipitating factor of sudden death.

Finally, rapid diagnostic tests are widely used for the management of RSV-infected patients. However, it was reported that the rapid antigen test had a low sensitivity at 60% and a specificity of 76%.[38] Therefore, the incidence of RSV-associated myocarditis might presently be underestimated.

Limitation

Endomyocardial biopsy and positive result for detection of virus are troublesome in patients who have bad condition. This study had limitations because of lacking of tissue biopsy to prove RSV infections in most cases. Therefore heart complication in RSV infection which caused by myocarditis is actual title.

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Author Contributions

HK designed the study; NI, SM and TN collected the data; HK wrote the manuscript; and NI, SN, GY and YK provided technical support and conceptual advice. All authors read and approved the final manuscript.

Declaration of Conflicting Interests

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Compliance with Ethical

All procedures performed in studies involving human participants were accordance with the ethical standards of the institutional and national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards (SH3841).

Informed consent was obtained from individual participants by any of the authors.

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