
Clinical report

Life-threatening extrapulmonary manifestations associated with respiratory syncytial virus infection in Japan

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Abstract

Objectives and methods : respiratory syncytial virus (RSV) is a common cause of childhood respiratory infection resulting in significant debilitation and mortality. In order to investigate the actual conditions of severe life-threatening RSV infections in Japan we handed out questionnaires and collected 29 severe cases with life-threatening cases from 9 institutes in Japan during three years.

Results : Eight out of the 29 life-threatening cases showed cardiopulmonary arrest. Two cases were diagnosed as myocarditis from bradycardia and cardiac failure. Four cases were diagnosed as encephalopathy. Cardiopulmonary arrest was caused by infection of the central nervous system and/or myocarditis.

Conclusion : In our study only 29 life-threatening were found, however, there are probably many more. A national survey of severe RSV infection should be conducted in order to clarify the actual condition.

Introduction

Respiratory syncytial virus (RSV) is a common cause

of childhood respiratory infection resulting in significant debilitation and mortality. While no cause of sudden infant death syndrome (SIDS) has been clearly

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identified, there is much evidence suggesting that RSV infections are related in some cases¹⁾²⁾. It is well known that premature birth, with or without or chronic lung disease, congenital heart disease, and T-cell immunodeficiency are conditions that predispose the subjects to more severe forms. Recently, cases of encephalopathy with RSV infection have been reported³⁾⁴⁾.

Methods

In order to investigate the actual condition of severe life-threatening RSV Infections we handed out questionnaires to 20 hospitals with pediatric emergency department and collected 29 cases with severe symptoms from nine institutes in Japan during 3 years. The severity was divided into 3 categories; severe respiratory failure, encephalopathy and myocarditis.

Results (table 1)

We received completed questionnaires from 9 pediatric departments. A total 29 cases (15 boys and 14 girls), aged from 20 days to 15 years old were collected. There were risk factors of low birth weight and underlying diseases (intrauterine growth retardation, congenital myopathy, ASD or patent foramen ovale (PFO), autoinflammatory disease). Nine cases out of 29 cases showed cardio-pulmonary arrest, including 2 cases without any symptoms before recognition. Four cases showed convulsion. The prognosis was very poor with 8 fatal cases and 3 severe sequelae (bedridden) cases. Cases diagnosed as encephalopathy had pleocytosis, increased IL-6, and were positive for RSV genome in cerebrospinal fluid (CSF) in 2 out of 3 cases. Subgroup A was detected in CSF by reverse transcription loop-mediated isothermal amplification⁵⁾. Patients with encephalopathy showed brain atrophy with no fatality. Two autopsies revealed one case with lung hemorrhage, destruction of bronchioles and spotty necrosis in the liver without any obvious changes in the brain (case 11), and one case with pneumonia with mucous blockage and gathering of pneumococci (case 25). Laboratory findings revealed that counts of white blood cells were mostly normal, and CRP showed mostly normal or low levels (less than 2 mg/dl). Hyponatremia was found in 2 out of 17 measured cases. There was no case which received anti-RS monoclonal antibodies (palivizumab).

Discussion

We presented 29 cases with severe RSV infection. Eight cases showed cardiopulmonary arrest. Two out of 3 showed abnormal findings in cerebrospinal fluid (pleocytosis, increases IL-6 and positive for virus). RSV is an extremely common cause of childhood respiratory infections, resulting in significant debilitation and

mortality. In this study we found many children with fatal infection who showed cardiopulmonary arrest (CPA) on arrival. Testing for RSV is not routinely done in Japan, therefore, there are obviously more cases reported as pneumonia of unknown origin or SIDS. Various hypotheses to explain SIDS have been postulated, such as maternal smoking, absence of breast-feeding, winter peak, prone sleeping position and poor socio-economic situation of families etc. While no cause has clearly been identified, there was much evidence suggesting that respiratory viral infections are related in some cases⁶⁾. Scott et al. reported that they detected respiratory viruses in 18%, and that 33% of these were RSV¹⁾. According to the report of Uren et al. 39% were positive for viruses, and of these 17% were RSV²⁾. The number of severe RSV infections is underestimated, and therefore we are not able to collect the questionnaires from 11 institutes. We recommend to develop a simpler and easier quick test.

In this study 2 cases were diagnosed as myocarditis from bradycardia and cardiac failure. RSV infection has been reported to be associated with acquired cardiovascular disease including arrhythmia and myocarditis⁷⁾. Sometimes dysrhythmia in infants causes cardiac failure⁸⁾. In this study two cases with myocarditis were diagnosed by their clinical symptoms. The patients with CPA in our study might also be correlated with myocarditis or arrhythmia.

Since RSV infection can have a fatal outcome in patients with congenital myopathy, we recommend anti-RS antibodies in patients with myopathy.

On the other hand, Van Steensel-Moll reported that in 64 admitted children with RSV infection, 39% had syndrome of inappropriate secretion of ADH (SIADH), two patients had symptoms followed by SIADH and two others had convulsions⁹⁾. Ng reported an incidence of encephalopathy of 1.8% in a total of 487 patients based on a study of a large number of children with RSV bronchiolitis in the United States³⁾. Seizures were the presenting complications¹⁰⁾. CPA or SIDS might have been caused by RSV infection of the central nervous system following SIADH.

The population parameter of RSV infection in Japan is unknown. In the United States each year an estimated 91,000 children are hospitalized, with 2,000 fatal cases. Eisenhut reviewed the extrapulmonary manifestations of severe respiratory syncytial virus infection, and pointed out endocrine effects and liver dysfunctions. In our study only 29 life-threatening cases were found, however there are probably many more. Therefore a national survey of severe RSV infection in Japan should be conducted in order to find out the actual occurrence and risks.

Table 1 profiles of patients with severe RS infection

	age	gender	underlying medical condition	birth weight (g)	symptoms	fever	cough	apnea	seizure	after effects	final diagnosis apart from bronchiolitis
1	20 day	M	none	unknown	respiratory distress	—	+	+	—	none	
2	24 day	M	none	3,516	respiratory distress	—	+	—	—	none	
3	24 day	M	TTN	2,742	respiratory distress, cyanosis	+	+	—	+	brain atrophy	encephalopathy
4	27 day	F	none	2,216	respiratory distress	—	+	+	+	brain atrophy	encephalopathy
5	1M	F	PFO	3,100	respiratory distress	—	+	—	—	none	
6	1M	F	ASD	2,930	respiratory distress	+	+	+	—	none	
7	1M	M	none	2,398	apnea	—	+	+	—	none	
8	1M	M	none	2,276	respiratory distress	+	+	—	—	none	
9	1M	F	none	2,496	respiratory distress	—	+	—	—	none	
10	1M	M	none	2,158	respiratory distress	—	+	+	—	mild	
11	1M	F	none	2,564	CPA	—	—	—	—	died	pulmonary hemorrhage
12	2M	M	none	unknown	CPA	—	—	—	—	died	
13	2M	M	none	2,496	respiratory distress	—	+	—	—	none	asthma
14	2M	F	none	2,158	respiratory distress	—	—	+	+	none	encephalopathy
15	2M	M	IUGR	1,386	CPA	—	+	—	—	died	
16	4M	M	unilateral kidney	3,246	CPA	+	+	—	+	bedridden	encephalopathy
17	5M	F	none	unknown	respiratory distress	+	+	—	—	under cardio-pulmonary support	myocarditis
18	8M	M	none	unknown	respiratory distress	+	+	—	—	none	adenovirus infection
19	8M	F	RDS	1,098	CPA	+	+	—	—	died	pneumonia
20	8M	F	Wilson-Mikity disease	1,098	CPA	+	—	—	—	died	
21	11M	F	none	3,186	respiratory distress	+	+	+	—	none	
22	1Y0M	M	none	3,078	respiratory distress	+	+	—	—	none	
23	1Y3M	M	none	unknown	unconsciousness	+	+	—	—	none	
24	1Y5M	M	PVL	876	respiratory distress	+	+	—	—	none	
25	2Y9M	F	none	3,425	CPA	+	—	—	—	died	pneumonia
26	2Y10M	F	congenital myopathy	2,416	CPA	+	+	—	—	bedridden	
27	5Y	M	congenital myopathy	2,612	CPA	+	—	—	—	died	
28	5Y4M	F	neonatal herpes simplex infection, cerebral palsy	unknown	brady- cardia	+	+	—	—	died	myocarditis
29	15Y	F	autoinflammatory disease	unknown	respiratory distress	+	+	—	—	bedridden	

CPA : cardiopulmonary arrest, TTN : transient tachypnea of newborn, PFO : patent foramen ovale, PVL : periventricular leukomalacia, IUGR : intrauterine growth retardation, RDS : respiratory distress syndrome

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本邦における RS ウイルス感染症における予後不良肺外合併症

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【要旨】 目的と方法 : Respiratory Syncytial Virus (以下 RSV) は、一部に予後不良な結果をきたす小児の呼吸感染症の代表的な原因ウイルスの一つである。本邦における致死的な重症 RSV 感染症の実態を知るため、3年間に於ける症例のアンケートを行い9つの施設から重症29例が収集できたので、その結果を解析する。

結果 : 致命的な症例として集められた29例中8例は、心肺停止を示していた。2例は徐脈と心不全からの心筋炎と診断、4例は脳症と診断されていた。心肺停止は中枢神経系の感染や心筋炎に起因することが推察された。

結論 : 9つの施設から容易に重症 RSV 感染症29例が収集できたことより、本邦において突然死を含め RSV 関連の重症例は相当数いることが推察された。このことから、今後はよりグローバルなレベルでの実態調査が必要と考えられた。

〈キーワード〉 脳症、心筋炎、RS ウイルス