Cardiopulmonary Manifestations of Fulminant Enterovirus 71 Infection

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ABSTRACT. Background. The pathogenesis of acute pulmonary edema and cardiac collapse after enterovirus 71 (EV71) infection are not completely understood. Objective. To determine the hemodynamic features and the mechanism of pulmonary edema (PE) after EV71 infection by direct intracardiac monitoring. Design. Prospective clinical and laboratory study at a tertiary medical center. Participants. Five consecutive infants, ages 2 to 13 months, with EV71 infection—proven by viral isolation in 4 and antibody in 1—with PE were enrolled. The clinical characteristics were systemically assessed. Hemodynamic profiles were determined every 4 hours by simultaneously implanted pulmonary arterial and central venous catheters during the acute stage. Results. Magnetic resonance imaging revealed that all 5 infants had brainstem lesions. All patients had tachycardia and hyperthermia. Transient systolic hypertension was noted in 1 patient, and 1 presented with hypotension. Pulmonary artery pressure in all 5 infants was normal or mildly elevated (26–31 mm Hg), and central venous pressure ranged from 10 to 22 mm Hg. Pulmonary artery occlusion pressures were normal or slightly elevated (13–16 mm Hg). Systemic and pulmonary vascular resistances were transiently increased in only 1 patient. The stroke volume index decreased to 15.3 to 35.7 mL/M² (normal: 30–60 mL/M²), but because of the elevated heart rate, the cardiac index did not decrease. All hemodynamics normalized within days. Conclusion. Fulminant EV71 infection may lead to severe neurologic complications and acute PE. The acute PE and cardiopulmonary decompensation in EV71 infection are not directly caused by viral myocarditis. The mechanism of PE may be related to increased pulmonary vascular permeability caused by brainstem lesions and/or systemic inflammatory response instead of increased pulmonary capillary hydrostatic pressure. Pediatrics 2002/109(2). URL: http://www.pediatrics.org/cgi/content/full/109/2/e26; enterovirus 71, pulmonary edema, pathogenesis, hemodynamics, hand-foot-mouth disease.

ABBR EV71, enterovirus 71; PE, pulmonary edema; PH, pulmonary hemorrhage; CNS, central nervous system; CK, creatine kinase; PAP, pulmonary artery pressure; PAOP, pulmonary artery occlusion pressure; CI, cardiac index; MRI, magnetic resonance imaging.

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catheter thermosensor. All hemodynamic measurements were repeated 3 times and the mean value recorded. The hemodynamic profiles were conducted every 4 hours until the hemodynamics became stable. In addition to intravenous immunoglobulin, intravenous inotropic agents of dobutamine (4–16 μg/kg/min) and milrinone (0.25–0.4 μg/kg/min) were used based on hemodynamic changes. Dopamine (4–16 μg/kg/min) was added if hypotension occurred.

All patients received brain magnetic resonance imaging (MRI) within 5 to 9 days after admission.

RESULTS

The 5 infants were males whose ages ranged from 2 to 13 months. Three of them had hand-foot-mouth disease, and 2 had herpangina. Three patients had suffered from myoclonic jerks and the other 2 had oculomotor paresis before onset of PE. All chest radiographs were initially normal and then, after the onset of PE, showed diffuse alveolar density without obvious cardiomegaly (Fig 1). All patients had the frothy secretion characteristic of PE, and 3 had evidence of PH, fresh blood from the endotracheal tube after intubation. Arterial blood gases showed hypoxemia and metabolic acidosis in all cases. All had peripheral blood leukocytosis with left shifting and platelet counts greater than 300 000/μL. Disseminated intravascular coagulation profiles (prothrombin time, partial thrombin time, fibrinogen, and fibrinogen degradation products) were within normal ranges, except for patient 2, who had prolonged prothrombin time (1.4 × normal) and partial thrombin time (1.9 × normal). The CK-MB/CK ratios ranged from 1.1% to 5.8% (mean: 3.7%). Cerebrospinal fluid examination showed pleocytosis, normal sugar level, and increased protein concentration. All patients showed variable degrees of bright signal changes in T2 images of the brainstem on MRI. The clinical manifestations, laboratory studies, and radiologic findings are summarized in Table 1.

Initial hemodynamic measurements are summarized in Table 2. Tachycardia was the most common finding. Therefore, although stroke volume index was below normal values (30–60 mL/M²) in 4 cases, the CI was not decreased because of the elevated heart beat. High fever was another common finding: 2 patients had central hyperthermia up to 41.5°C. PAP was normal or mildly elevated (26–31 mm Hg in systole) and <40% of systemic pressure in all patients. Central venous pressure ranged from 10 to 22 mm Hg. PAOP was normal or slightly elevated (13–16 mm Hg). During admission, only 1 patient (patient 4) had transient systolic hypertension (up to 140/66 mm Hg) and transient increase of both systemic and pulmonary vascular resistance. Another (patient 2) had transient hypotension (65/34 mm Hg) and decreased systemic vascular resistance, whereas the other 3 patients had normal blood pressure and vascular resistance. The CI was maintained in normal range throughout the study (range: 3.1–6.9 L/min/M²). All cardiac hemodynamic profiles became stable within 48 hours after admission when PE resolved (Fig 2).

The 2 patients (patients 3 and 4) who presented with mild PE without hemorrhage and with minimal brainstem lesions recovered with minimal neurologic sequelae. The other 3 patients, who presented with PE, PH, and extensive brainstem lesions, remained respirator-dependent and physically inactive most likely because of the lesions.

DISCUSSION

The most important findings of the present study are that 1) EV71 infection can lead to severe neurologic complications and acute PE with or without hemorrhage; 2) all patients with EV71 infection and PE had brainstem lesions; 3) viral myocarditis is not the direct cause of acute PE and cardiopulmonary failure in EV71 infection; and 4) the excessive central sympathetic activation resulting in vasoconstriction was not the major cause of PE or hemorrhage.

A strong etiologic link between EV71 and the histologic changes in the CNS is well-established.1–6 However, the pathogenesis of PE in EV71 is still unknown. The autopsy findings and brain MRI stud-
<table>
<thead>
<tr>
<th>Patient</th>
<th>Sex/Age</th>
<th>Clinical Features</th>
<th>CSF Findings (WBC/Pro/Glu)</th>
<th>CXR Findings</th>
<th>MRI Findings</th>
<th>CTR</th>
<th>PE and PH</th>
<th>PAOP</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>M/8</td>
<td>HFMD, fever for 4 d; myoclonic jerk for 2 d; poor response for 3 h</td>
<td>120/76/71</td>
<td>PE and PH</td>
<td>Diffuse T2 bright signal at the brainstem and upper brain</td>
<td>CTR:0.47</td>
<td>Throat</td>
<td>PE and PH</td>
<td>Recovery</td>
</tr>
<tr>
<td>2</td>
<td>M/5</td>
<td>Herpangina, fever for 3 d; lethargy for 3 h</td>
<td>33/84/92</td>
<td>CTR:0.5</td>
<td>T2 bright signal at parietal cortex, and upper spinal cord</td>
<td>Diffuse T2 bright signal at posterior pons</td>
<td>Stool</td>
<td>PE and PH</td>
<td>Minor sequelae</td>
</tr>
<tr>
<td>3</td>
<td>M/13</td>
<td>HFMD, fever for 6 d; myoclonic jerk for 3 h, consciousness change</td>
<td>128/35/73</td>
<td>CTR:0.5</td>
<td>Mild T2 bright signal at posterior pons</td>
<td>Mild T2 bright signal at posterior pons and upper spinal cord</td>
<td>PE and PH</td>
<td>PE and PH</td>
<td>Minor sequelae</td>
</tr>
<tr>
<td>4</td>
<td>M/11</td>
<td>HFMD, fever for 6 d; lethargy, tachypnea for 4 h</td>
<td>26/35/64</td>
<td>CTR:0.5</td>
<td>PE and PH</td>
<td>PE and PH</td>
<td>Antibody titer increase</td>
<td>PE and PH</td>
<td>Minor sequelae</td>
</tr>
<tr>
<td>5</td>
<td>M/2</td>
<td>Herpangina, fever for 3 d; lip cyanosis with upward gaze for 30 min</td>
<td>291/98/102</td>
<td>CTR:0.46</td>
<td>PE and PH</td>
<td>PE and PH</td>
<td>Stool</td>
<td>PE and PH</td>
<td>Minor sequelae</td>
</tr>
</tbody>
</table>

HFMD indicates hand-foot-mouth-disease; CSF, cerebrospinal fluid; WBC, white blood cell count (/(mm³); Pro, protein (mg/dL); Glu, glucose (mg/dL); CXR, chest radiograph; CTR, cardiothoracic ratio.

Persistent high fever and tachycardia were the most common findings in these patients. Usually, when the fever subsided, the heart rate slowed down, which also suggested that the tachycardia might have been caused by hyperthermia and not from increasing sympathetic activities resulted from compensatory response to heart failure.

The reticular formation of the medulla, a vasomotor center, when damaged can result in autonomic nervous dysfunction and rapid cardiovascular collapse. In previous reports, patients with bulbar poliomyelitis also had an acute onset of PE and similar brain autopsy findings. Therefore, we believe it is reasonable to deduce that the reticular formation may be responsible for the occurrence of PE and acute cardiac collapse. Severity of damage to this area is also closely associated with clinical outcome in these patients.

Regarding the mechanisms of neurogenic PE, previous studies have emphasized the role of massive central sympathetic neural discharge. This massive discharge leads to peripheral vasoconstriction and displacement of blood from the periphery to the heart and pulmonary vascular bed. Consequently, the patient will have increased pulmonary capillary pressure and edema formation. PE could develop rapidly after massive central sympathetic activation, but the pulmonary vascular pressure had to increase to very high levels before severe PE developed. When arterial vasoconstriction develops, it may result in hypertension and secondary cardiac dysfunction. Some patients with severe EV71 infection had transient hypertension before acute onset of PE and decreased left ventricular ejection fraction by echocardiogram. However, we found that by direct cardiac monitoring, all 5 patients—who had acute PE—had normal or very mildly elevated PAOP and PAP. Only 1 patient (patient 4) had a transient increase of pulmonary vascular resistance index and systemic vascular resistance index. This may suggest that the development of acute PE may not be fully explained by the sympathetic storm after the brainstem injury. In this study, intravenous dobutamine was immediately given routinely when the patient had PE. Although the vasodilating effect of dobutamine may somewhat influence vascular resistance, the interference may be minimal because of the short delay before Swan-Ganz catheter insertion. Milrinone and dopamine were prescribed later based on the intracardiac he-
modynamic changes, so they should have had no direct effect on the initial cardiac hemodynamics.

Pulmonary edema can develop because of increasing hydrostatic pressure or alveolar-capillary membrane permeability of the lungs. Evidence indicates that the CNS lesion also could alter the pulmonary vascular permeability and result in PE.\textsuperscript{17–20} Severe systemic infection could induce the release of various cytokines, which may cause lung injury that increases pulmonary permeability.\textsuperscript{21} All our patients had high fever, tachycardia, tachypnea, and leukocytosis with left shifting, compatible with the features of systemic inflammatory response syndrome.\textsuperscript{22} Based on our observations, the pathogenesis of PE after fulminant EV71 infection may be related to increased pulmonary vascular permeability instead of increased pulmonary capillary hydrostatic pressure.

The management of PE and PH in patients with EV71 is important but difficult. Based on the hemodynamic profile found in this study, we have the following suggestions: 1) Because PE in EV71 infection is not resulting from excessive vasoconstriction alone, vasodilators should be used with caution; 2) cardiopulmonary function usually returns to nearly normal within days, but the neurologic sequelae are severe and usually permanent. Therefore, the use of extracorporeal membrane oxygenation support or a left heart assist device should be weighed carefully; and 3) direct intracardiac hemodynamic monitoring.

### Table 2. Initial Hemodynamic Measurement in Patients With EV71

<table>
<thead>
<tr>
<th>Patient 1</th>
<th>Patient 2</th>
<th>Patient 3</th>
<th>Patient 4</th>
<th>Patient 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>CT °C</td>
<td>41.6</td>
<td>41.5</td>
<td>38.4</td>
<td>38.9</td>
</tr>
<tr>
<td>HR bpm</td>
<td>202</td>
<td>217</td>
<td>167</td>
<td>152</td>
</tr>
<tr>
<td>BP (S/D/M) mm Hg</td>
<td>101/40/60</td>
<td>65/34/44</td>
<td>107/73/81</td>
<td>141/66/91</td>
</tr>
<tr>
<td>PAP (S/D/M) mm Hg</td>
<td>29/24/26</td>
<td>26/19/21</td>
<td>29/21/23</td>
<td>31/23/25</td>
</tr>
<tr>
<td>CVP mm Hg</td>
<td>22</td>
<td>10</td>
<td>15</td>
<td>12</td>
</tr>
<tr>
<td>PAOP mm Hg</td>
<td>14</td>
<td>13</td>
<td>16</td>
<td>15</td>
</tr>
<tr>
<td>Cl L/min/m²</td>
<td>3.93</td>
<td>4.53</td>
<td>6.01</td>
<td>2.32</td>
</tr>
<tr>
<td>SI mL/m²</td>
<td>19.5</td>
<td>20.9</td>
<td>35.7</td>
<td>15.3</td>
</tr>
<tr>
<td>SVRI dyne/s/cm²/m²</td>
<td>779</td>
<td>600</td>
<td>826</td>
<td>2720</td>
</tr>
<tr>
<td>PVRI dyne/s/cm²/m²</td>
<td>244</td>
<td>141</td>
<td>133</td>
<td>344</td>
</tr>
<tr>
<td>LVSWI gm/m²</td>
<td>12.2</td>
<td>8.8</td>
<td>31.5</td>
<td>15.8</td>
</tr>
<tr>
<td>RVSWI gm/m²</td>
<td>1.06</td>
<td>3.12</td>
<td>3.88</td>
<td>2.70</td>
</tr>
</tbody>
</table>

CT indicates core temperature; HR, heart rate; BP, blood pressure; S/D/M, systolic/diastolic/mean; CVP, central venous pressure; SI, stroke index; SVRI, systemic vascular resistance index; PVRI, pulmonary vascular resistance index; LVSWI, left ventricular stroke work index; RVSWI, right ventricular stroke work index.

### Fig 2. A, Sequential changes over 48 hours of PAOP; B, CI; C, pulmonary vascular resistance, and D, systemic vascular resistance.
may provide additional information to guide critical care.

CONCLUSION

Acute PE may be related closely to increased pulmonary vascular permeability caused by brainstem lesions and/or severe viral infection. Acute cardiopulmonary decompensation in patients with fulminating EV71 infection, however, is not caused by myocarditis itself but most probably by the damage to the vasomotor center of the brainstem. The excessive central sympathetic activation resulting in vasoconstriction was not the major cause of PE or PH.

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REFERENCES

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