The Follow-up Evaluation of Electrocardiogram and Arrhythmias in Children With Fulminant Myocarditis

Rie Ichikawa, MD; Naokata Sumitomo, MD, PhD; Akiko Komori, MD; Yuriko Abe, MD; Takahiro Nakamura, MD; Junji Fukuhara, MD; Masaharu Matsumura, MD; Michio Miyashita, MD, PhD; Hiroshi Kanamaru, MD; Mamoru Ayusawa, MD, PhD; Hideo Mugishima, MD, PhD

Background: Fulminant myocarditis involves various serious arrhythmias that sometimes have lethal consequences. The purpose of the present study was to investigate the electrocardiogram findings, arrhythmogenicity and abnormalities of the cardiac conduction system in children with fulminant myocarditis.

Methods and Results: Between 1999 and 2008, 7 consecutive patients (mean age: 7 years) who suffered from fulminant myocarditis were included in the study. A 12-lead electrocardiogram, Holter monitoring and signal-averaged electrocardiograms were performed and compared between the acute, convalescent, and recovery phases in the 4 surviving patients. Also, electrophysiologic assessment was carried out during the convalescent phase. Five out of 7 patients developed complete atrioventricular block, 3 developed ventricular tachycardia, 2 had cardiac arrest, 2 developed sinus tachycardia, 1 developed ventricular fibrillation, 1 had advanced atrioventricular block, and 1 developed sick sinus syndrome. Among the surviving patients, all arrhythmias resolved during the convalescent and remote phases. No atrial or ventricular arrhythmias were induced in any patients during the programmed stimulation study. In the convalescent phase, no arrhythmias could be induced and there were no signs of any conduction abnormalities on electrophysiologic assessment.

Conclusions: Close follow-up should be performed to observe for the occurrence of any new arrhythmias and/or a decrease in cardiac function in children with fulminant myocarditis. (Circ J 2011; 75: 932–938)

Key Words: Atrioventricular block; Fulminant myocarditis; Ventricular fibrillation; Ventricular tachycardia

F ulminant myocarditis is defined as an acute onset of myocarditis in which the patient cannot maintain adequate cardiac circulation without some kind of mechanical cardiopulmonary support (CPS). Fulminant myocarditis is associated with a wide variety of serious arrhythmias such as advanced or complete atrioventricular block, ventricular tachycardia (VT), ventricular fibrillation (VF), which sometimes have lethal consequences because the condition is associated with severe congestive heart failure and sometimes cardiogenic shock due to left ventricular myocardial dysfunction. The prognosis in those patients who overcome the acute phase, however, is relatively good despite the serious conditions during that phase. The purpose of the present study was to investigate the arrhythmogenicity and abnormalities of the cardiac conduction system in children recovering from fulminant myocarditis and to assess for the risk of future arrhythmias.

Methods

Between 1999 and 2008, 7 consecutive patients with fulminant myocarditis (mean age 7 years, M:F=4:3) were hospitalized and placed in the intensive care unit of the Department of Pediatrics at Nihon University School of Medicine (Table 1). Congenital heart disease, myocardial infarctions, cardiac tumors, autoimmune disease, rheumatic fever, and neuromuscular disease were excluded on subsequent serological tests, echocardiograms and electrocardiograms.

Four out of the 7 patients (patients 1–4) survived the acute phase of the fulminant myocarditis with the use of mechanical CPS. Three patients (patients 5–7) died before any CPS could be performed. All the patients were diagnosed with fulminant myocarditis based on decreased cardiac contractility with a left ventricular ejection fraction (LVEF) of <0.20, severe cardiomegaly with a cardiothoracic ratio of >0.60, presence of life-threatening arrhythmias, and elevated biomarkers, including the serum MB isoform of creatine kinase.
(CK-MB) and troponin T. A detailed medical history was obtained from the parents or guardians, and a complete physical examination was carried out. A chest X-ray, echocardiogram, and 12-lead electrocardiogram were obtained in every patient. Ambulatory 24-h electrocardiogram monitoring and a signal-averaged electrocardiogram were performed, and the findings were compared between the acute, convalescent, and remote phases in the surviving patients. The thickness of the left ventricular posterior wall at end diastole (LVPWd) was measured on echocardiography and expressed as the percentage of the normal value revised using body surface area.11

Paired serological tests to find any potential causes of viral infections were also performed in the surviving patients. Parainfluenza type 3 virus was detected in patient 4, but no other viruses were detected in any other patients.

A myocardial biopsy was performed in the acute phase when patients 1, 2 and 3 underwent open chest CPS. Pathological findings were obtained from the autopsy specimens in patients 5 and 7.

On admission, 3 patients were intubated and 1 had already been intubated prior to arrival due to unresponsiveness and cardiogenic shock. Advanced and/or complete atrioventricular block with premature ventricular contractions were noted in 3 patients, and 2 patients had repetitive asystole, and required pacing promptly. One patient had VT that progressed to VF the next day. In all 4 patients, these arrhythmias improved immediately after beginning CPS and for up to 24 h afterwards. All 4 patients required mechanical CPS and temporary VVI pacing to maintain their cardiac function. The CPS circuit consisted of a centrifugal pump and heparin-coated circulating system. The size of the venous extraction line was 14–22 Fr, and the arterial drain line was 14–17 Fr. Three patients underwent open chest CPS, and a 13-year-old boy underwent percutaneous CPS. Also, steroid pulse therapy, high-dose gamma globulin, dopamine, dobutamine and phosphodiesterase III inhibitor treatments were performed in all patients. The clinical details and management of those patients have been previously reported elsewhere.12

Electrophysiologic Assessment

After obtaining written informed consent from the patients’ guardians, electrophysiologic assessment was carried out during the convalescent phase (28.5±11.2 days after onset) under mild i.v. anesthesia to confirm the lack of a need for antiarrhythmic therapy or pacemaker implantation. Quadrupolar electrode catheters were introduced via the femoral, cervical, or subclavian veins and positioned in the right ventricle, high right atrium, and septal leaflet of the tricuspid valve for electrocardiography and to pace the right atrium and right ventricle.

Programmed right atrial pacing was performed to induce atrial arrhythmias. Programmed ventricular stimulation up to triple extrastimuli from the right ventricular apex and right ventricular outflow tract was also performed to induce VT or VF. The sinus node function and atrioventricular conduction properties were also evaluated.

Results

Prognosis

Three patients died before any CPS could be performed. The electrocardiograms showed sinus rhythm when those patients were hospitalized, but they developed progressive bradycardia and we could not resuscitate them despite maximum efforts. The other 4 patients were successfully resuscitated using aggressive pharmacological and mechanical support.

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age</th>
<th>Gender</th>
<th>Arrhythmia</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>5</td>
<td>F</td>
<td>VT, CAVB, cardiac arrest</td>
</tr>
<tr>
<td>2</td>
<td>6</td>
<td>F</td>
<td>VT, VF, CAVB</td>
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<tr>
<td>3</td>
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<td>CAVB, cardiac arrest</td>
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<td>13</td>
<td>M</td>
<td>CAVB, VT</td>
</tr>
<tr>
<td>5</td>
<td>3</td>
<td>M</td>
<td>Sinus tachycardia, CAVB</td>
</tr>
<tr>
<td>6</td>
<td>9</td>
<td>M</td>
<td>Sinus tachycardia, sick sinus</td>
</tr>
<tr>
<td>7</td>
<td>15</td>
<td>M</td>
<td>Advanced AVB</td>
</tr>
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Every patient had some kind of life-threatening arrhythmia. VT, ventricular tachycardia; CAVB, complete atrioventricular block; VF, ventricular fibrillation; AVB, atrioventricular block.

Figure 1. Histopathological findings. (a) Endomyocardial biopsy from patient 3. There is extensive interstitial lymphocytic infiltration. Although myocyte damage is apparent, no intermyocardial fibrosis is present. These findings correspond to the active myocarditis (hematoxylin and eosin (HE); magnification x40). (b) Myocardial autopsy specimen from patient 5. Severe infiltration of inflammatory cells, atrophy and necrosis of the myocytes were identified. These findings represent active myocarditis (HE; magnification x40). (c) Myocardial autopsy specimen from patient 7. Granulomatous changes and fibrosis have begun in this specimen. This finding suggests myocarditis in the chronic phase (HE; magnification x40).
Figure 2. Electrocardiogram parameter changes in each patient. There were no statistically significant changes in any of the electrocardiogram parameters. Patient 1 had a prolonged PR interval, but the other 3 patients developed complete atrioventricular block. After recovering from the myocarditis, all electrocardiographic parameters returned to normal except for the QRS duration in patient 3, who developed complete right bundle branch block. Gray, abnormal range. HR, heart rate; PR, PR interval; QRS, QRS duration; QT, QT interval; QTc, corrected QT interval.
Histopathology
From the histopathological findings in the acute phase (patients 1–3), and at autopsy (patients 5 and 7), severe interstitial inflammatory cell infiltration and destruction of the myocardial cells was found in all specimens (Figure 1). These findings confirmed myocarditis.

Electrocardiography
The electrocardiogram measurements were compared between the acute phase and convalescent phase (Figure 2). It was not possible to measure the PR duration in 3 patients because of complete atrioventricular block. In regard to the bradyarrhythmias, each patient’s heart rate increased during the convalescent phase, but not statistically significantly due to the limited number of patients. The QT interval, QTc interval and QRS duration were compared during the acute, convalescent and remote phases. Although QT interval and QTc interval remained unchanged, the QRS duration became shorter during the convalescent and remote phases in all patients, but this was not statistically significant (Figure 2). Patient 3 developed complete right bundle branch block after recovering from the fulminant myocarditis (Figure 3).

Clinical Arrhythmias
The clinical arrhythmias in the present patients are summarized in Table 1. Five out of 7 patients developed complete atrioventricular block, 3 developed VT, 2 developed asystole, 2 developed sinus tachycardia, 1 developed VF, 1 had advanced atrioventricular block, and 1 developed sick sinus syndrome (Table 1). Among the surviving patients, all these arrhythmias resolved during the convalescent and remote phases.

In patient 2, an electrocardiogram had been recorded during a medical examination for entering school 5 months prior to the admission. The electrocardiogram exhibited normal sinus rhythm.

Holter Electrocardiogram
A Holter electrocardiogram was recorded in 3 patients during the acute phase (10.3±3.8 days after onset) and convalescent phase (24.3±10.4 days after onset; Figure 4). One patient had 4 beats of VT during the acute phase. None of the patients

Figure 3. Electrocardiographic changes in patient 3. (Upper panel) Electrocardiogram prior to admission exhibiting normal sinus rhythm without any right bundle branch block. (Lower panel) Electrocardiogram recorded after the patient had recovered from the fulminant myocarditis, in which sinus rhythm with complete bundle branch block was observed.
Figure 4. Holter monitoring parameter changes in each patient. The total heart beats and maximum RR interval did not change significantly. One patient had 4 beats of ventricular tachycardia during the acute phase. In patient 3 the number of premature ventricular contractions and premature atrial contractions increased during the convalescent phase. HB, heart beat; PAC, premature atrial contraction; PVC, premature ventricular contraction.

Figure 5. Parameters of the signal averaged electrocardiogram in the acute and remote phases were normal except for in patient 2. In patient 2 the RMS40 was 9.3 μV (normal >20 μV); LAS40, 59 ms (normal <40 ms); and fQRS, 127 ms (normal <120 ms). The ventricular late potentials were determined to be positive because all these 3 parameters were abnormal in this patient. The RMS40 and LAS40 returned to normal in the convalescent phase. Gray, abnormal range. fQRS, total filtered QRS duration; LAS40, duration of the low-amplitude electric potential component of the terminal portion of the QRS; RMS40, root mean square voltage of the 40-ms terminal portion of the QRS.
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had any VT or supraventricular tachycardia episodes during the convalescent phase.

Late Potentials

A signal-averaged electrocardiogram was recorded in the surviving patients during the acute phase (10±3 days after onset) and remote phase (2,190±1,171 days) after onset (Figure 5). The root mean square voltage of the 40-ms terminal portion of the QRS (RMS40), duration of the low-amplitude electric potential component of the terminal portion of the QRS (LAS40) and total filtered QRS duration (fQRS) were measured. Only 1 patient (patient 2) had a positive late potential during the acute phase (Figure 5) and it disappeared during the convalescent phase. The other 3 patients had negative late potentials during the acute and convalescent phases.

Electrophysiologic Assessment

Electrophysiologic assessments were performed in all 4 survivors. The sinus node recovery time, corrected sinus node recovery time, and sinoatrial conduction time were all within normal limits (Table 2). The atrioventricular nodal effective refractory period and Wenckebach rate were within normal limits in all patients (Table 2).

No VT or VF could be induced in any of the patients. No atrial fibrillation, atrial flutter, or any other atrial tachycardia could be induced by programmed atrial stimulation.

Echocardiography

We performed sequential 2-D echocardiography in 4 survivors, and evaluated the LVEF and LVPWd during the acute, convalescent, and remote phases (Figure 6). Both the LVEF and LVPWd were very impaired in the acute phase, but markedly improved during the convalescent phase.

Discussion

The Dallas criteria have been widely used for the pathologic definition and classification of myocarditis. The criteria used to define fulminant myocarditis are myocarditis associated with a severe hemodynamic compromise requiring high doses of vasopressors (>5 μg dopamine or dobutamine per kg body weight per min) or a left ventricular assist device. All of the present patients met these criteria. The incidence of fulminant myocarditis has been reported to be as low as 11% of all types of myocarditis.

Despite the severity of the illness during the acute phase of the fulminant myocarditis, it is likely that the left ventricular function recovered more than it would have in acute myocarditis, due to aggressive pharmacological and mechanical support.

Various arrhythmias have been documented during the acute phase of fulminant myocarditis, such as sinus arrest, atrioventricular block, VT, and VF. Most of those arrhythmias resolved following the hemodynamic recovery of the myocarditis. The cardiac dysfunction and wall thickness in the acute phase improved in the convalescent phase. LVEF, left ventricular ejection fraction; LVPWd, left ventricular posterior wall thickness at end diastole.
ventricular late potentials during the acute phase subsequently disappeared during the convalescent phase, along with the disappearance of the ventricular arrhythmias. In a similar manner, the cardiac dysfunction and ventricular wall thickness in the acute phase improved in the convalescent phase.

The aforementioned points suggest that the arrhythmias observed during the acute phase of the fulminant myocarditis were due to a transient inflammatory cell infiltration of the myocardium, and edema of the myocardial cells and intermyocardial cellular space, which may have caused transient conduction block of the myocardial conduction system, or uniformity of the refractory period of the myocardium. These findings disappeared during the recovery phase of the fulminant myocarditis, but some patients continued to have ST abnormalities and bundle branch block. Di Bella et al analyzed the myoccardial wall motion with the use of cardiac magnetic resonance imaging and 2-D strain echocardiography in acute focal myocarditis with epicardial damage, and found that there were no wall motion abnormalities, although the longitudinal and circumferential function was impaired in those patients. In the present patients the LVEF improved to within the normal range during follow-up, but focal damage may still have existed in those patients. In those patients, close follow-up was required to determine the possible cause of the arrhythmic events or failure of the cardiac function.

To sum up, various bradyarrhythmias and tachyarrhythmias developed during the acute phase and resolved during the convalescent and remote phases, as confirmed on electrocardiogram and Holter monitor follow-up. On electrophysiological assessment during the convalescent phase, no arrhythmias could be induced and there were no signs of any conduction abnormalities. Similarly, the LVEF improved in the convalescent phase.

**Conclusion**

Close follow-up including 12-lead electrocardiogram, Holter monitoring, and echocardiography, should be carried out to observe for the occurrence of any new arrhythmias and/or a decrease in the cardiac function.

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