Detection and Evaluation of Asymptomatic Myocarditis in Schoolchildren*

Report of Four Cases

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**Study objective:** Data on the prevalence of myocarditis in children are limited. Autopsy studies have shown that myocarditis is often undiagnosed. We attempted to investigate the clinical features of asymptomatic myocarditis in four schoolchildren detected during a mass ECG screening in schoolchildren.

**Design and setting:** To evaluate asymptomatic myocarditis, we clinically examined 12 schoolchildren who were referred to Shiga University of Medical Science Hospital, Otsu, Japan, because of abnormal ST or T waves detected during ECG screening. None of the 12 children had experienced any episodes suggesting cardiac disease or Kawasaki disease. Cardiac function and myocardial viability were assessed by two-dimensional echocardiography (2-DE), thallium-201 (201Tl) myocardial scintigraphy, and cardiac catheterization. Endomyocardial biopsy specimens were examined histologically.

**Patients:** Endomyocardial biopsy specimens revealed histologic evidence of myocarditis in 4 of the 12 children with abnormal ST or T waves.

**Results:** Abnormal tracer perfusion was observed on 201Tl myocardial scintigrams in these four children, but the results of coronary arteriography were normal. 2-DE showed left ventricular hypokinesis in one child and left ventricular enlargement in one of the four children with histologic evidence of myocarditis. A second endomyocardial biopsy specimen was obtained in two of four children, showing persistent myocarditis in one child.

**Conclusions:** This type of screening program and indepth evaluation using 2-DE and 201Tl myocardial scintigraphy appear to be helpful in identifying children with myocarditis. The present histologic investigations suggested that even asymptomatic myocarditis might result in persistent heart damage.

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**Key words:** asymptomatic myocarditis; electrocardiography; schoolchildren; screening; two-dimensional echocardiography; 201Tl myocardial scintigraphy

**Abbreviations:** CAG = coronary arteriography; CI = cardiac index; 2-DE = two-dimensional echocardiography; SPECT = single-photon emission CT; 201Tl = thallium-201

Accurate clinical data on myocarditis in children are limited because of the possibility of undiagnosed asymptomatic myocarditis. We detected myocarditis in four asymptomatic schoolchildren during an ECG mass examination at school. We report here the clinical and laboratory findings in these four cases of asymptomatic myocarditis to clarify the characteristics of this disease.

**Materials and Methods**

**Patients**

ECG examinations conducted by the Japanese Ministry of Education have been performed in schools in Japan since 1978 to detect undiagnosed heart disease and to protect schoolchildren against sudden cardiac death. In the Shiga Prefecture in 1995, 44,968 of 45,112 children in the first, fourth, and seventh grades had a screening ECG. Further cardiac examinations were rec-
ommended in 2,559 of them (5.6%), including children with a history of Kawasaki disease. Of the 298 schoolchildren who were referred to Shiga University of Medical Science Hospital as part of this program in 1995, 12 demonstrated abnormal ST or T waves in some leads. None had experienced any episode that would suggest the presence of cardiac disease or Kawasaki disease. Cardiac function and myocardial viability were evaluated in these 12 children by two-dimensional echocardiography (2-DE), thallium-201 (201Tl) myocardial scintigraphy, coronary arteriography (CAG), left ventriculography, and cardiac index (CI) calculated by the thermodilution method. Endomyocardial biopsy specimens were also obtained and examined histologically. Informed consent was obtained from the subjects’ parents for 2-DE, 201Tl myocardial scintigraphy, CAG, and endomyocardial biopsies.

The other 286 children included 42 patients with some congenital heart disease, 36 with a history of Kawasaki disease, 41 with premature supraventricular contraction, 30 with premature ventricular contraction, 13 with marked sinus arrhythmia, 16 with first-degree and Wenckebach-type atrioventricular block, 15 with right bundle branch block, 4 with QT prolongation, 5 with preexcitation syndrome, 4 with left-axis deviation, 22 with right-axis deviation, 46 with left ventricular hypertrophy, 3 with right ventricular hypertrophy, 1 with Q8 pattern in lead V1, and 3 with deep Q waves in the left precordial leads. None, except for the five patients with preexcitation syndrome, had abnormal ST or T waves. These children also had adequate detailed examinations including chest radiography, 2-DE, 24-h ambulatory ECG recording, and treadmill exercise ECG. These examinations revealed no signs of myocardial damage, ventricular tachyarrhythmia, and advanced atrioventricular block in the 286 children. Three of four children with QT prolongation had a family history of QT prolongation, and the other one showed normal value of corrected QT interval during exercise and 24-h ECG recording.

**ECG Criteria**

ST- and T-wave abnormalities were defined according to the criteria established by the Japanese Society of Pediatric Cardiology and Cardiac Surgery.1 An abnormal ST segment was defined as a segment showing a >0.5-mm horizontal or downslope depression in any of the following leads: I, II, aVL, aVF, or V1 to V6. A negative or biphasic T wave >1 mm in leads I, II, aVL (when the R-wave amplitude is >5 mm), aVF (when the QRS complex is positive), or V4 to V6 was defined as abnormal.

**Criteria for an Abnormal Result on 201Tl Myocardial Perfusion Scintigraphy**

Single-photon emission CT (SPECT) images were inspected visually by three observers and analyzed quantitatively by the reconstructed polar tomograms. Each observer blindly evaluated the initial and delayed images using a scoring system as follows: 1 = normal, 2 = equivocal, and 3 = low perfusion. For the quantitative analysis of SPECT images, the short-axis slices from the first slice with apical activity to the last slice with activity at the base were used. Their count profiles were generated by computer software and plotted onto a two-dimensional volume-weighted polar map, which was then divided into 13 segments matching ECG segments. Using an automated computer procedure, the segment with maximal activity was normalized to 100, and the activity of the other segments was expressed as a percentage of the peak activity segment. Abnormal perfusion was defined as <70% of the maximal 201Tl accumulation.

**Endomyocardial Biopsy**

To avoid false-negative findings, at least five specimens were obtained from the right ventricular apex of each child. Using the Dallas criteria,4 we investigated the presence of findings characteristic of myocarditis, such as fibrosis, fatty infiltration, myocardial degeneration, and hypertrophy. Specimens were considered positive for infiltrating inflammatory cells when >5 mononuclear cells were detected per microscope field magnified by 400.

**Results**

Endomyocardial biopsy specimens revealed histologic evidence of myocarditis in 4 of 12 children with abnormal ST or T waves and right ventricular dysplasia in 1 child. These five children also demonstrated perfusion abnormalities on 201Tl myocardial scintigraphy. However, CAG showed no abnormalities of the coronary arteries in these five children. 2-DE showed left ventricular hypokinesis in one of these five children and left ventricular enlargement in one child. Echocardiography also revealed marked right ventricular enlargement and left ventricular hypokinesis in the patient with right ventricular dysplasia. ECG of this patient showed a right-axis deviation and incomplete right bundle branch block as well. We excluded this patient from our estimation of myocarditis because although his biopsy specimens showed abundant fatty infiltration, there were <5 mononuclear cells per field.

Endomyocardial biopsy specimens, 201Tl myocardial scintigraphy, and 2-DE showed no abnormal findings in the other seven children. Five of the seven children had ST depression and negative T waves in either lead II or aVF, or in both of them, but no abnormal ST or T waves in leads V4 to V6. One of other two children showed negative T waves in leads V1 to V4 without ST depression, and the other one had biphasic T waves in lead II and negative T waves in leads III, aVF, and V1 to V4.

There were a few discrepancies among observers in scoring each segment in the images of myocardial scintigraphy. However, as the discrepancies were recognized only in determining whether equivocal or low perfusion was present in the apical area, they were resolved by consensus and made no decisive effect on the final diagnosis.

**Case Reports**

**Patient 1:** This 7-year-old Japanese boy had negative T waves in leads III, aVF, and V1 to V5 (Fig 1). A chest radiograph revealed mild cardiomegaly, with a cardiothoracic ratio of 58%. 2-DE disclosed left ventricular hypofunction (fractional shortening, 0.18; ejection fraction, 0.35) and hypokinesis in the anteroapical wall by segmental analysis. However, nei-
ther enlargement of the left ventricle nor myocardial thickening was detected (left ventricular end-diastolic diameter, 34 mm; left ventricular posterior wall thickness, 5.5 mm). Myocardial scintigraphy showed low perfusion of the tracer in the apex (Fig 2). Cardiac catheterization revealed mildly elevated left ventricular end-diastolic pressure (12 mm Hg), but CI (3.9 L/min/m²) and aortic pressure (102/65 mm Hg; mean, 83 mm Hg) were shown to be normal. Although the results of CAG were normal, a left ventriculogram disclosed hypokinesis in the anterolateral wall. This hypokinetic site was congruent with the area of low perfusion on the myocardial scintigram. Biopsy specimens from the right ventricular apex revealed mild myocardial degeneration and inflammatory cell infiltration in the interstitial tissue, especially in the perivascular area. An ECG recorded 1 year later was normal, and a subsequent endomyocardial biopsy specimen showed a decreased number of infiltrating inflammatory cells.

Patient 2: This 9-year-old Japanese girl was referred to us because of negative T waves in leads II, III, aVF, and V1 to V5. No abnormal findings had been detected on previous ECG obtained when she was 6 years old. A chest radiograph showed no cardiomegaly or pulmonary congestion, but 2-DE showed a mildly enlarged left ventricle with an end-diastolic diameter of 44 mm. The left ventricle was not hypokinetic (fractional shortening, 0.37) and no segment wall-motion abnormalities were detected. Cardiac catheterization revealed mildly elevated left ventricular end-diastolic pressure (13 mm Hg), but CI (3.9 L/min/m²) and aortic pressure (102/65 mm Hg; mean, 83 mm Hg) were shown to be normal. Although the results of CAG were normal, a left ventriculogram disclosed hypokinesis in the anterolateral wall. This hypokinetic site was congruent with the area of low perfusion on the myocardial scintigram. Biopsy specimens from the right ventricular apex revealed mild myocardial degeneration and inflammatory cell infiltration in the interstitial tissue, especially in the perivascular area. An ECG recorded 1 year later was normal, and a subsequent endomyocardial biopsy specimen showed a decreased number of infiltrating inflammatory cells.

Patient 3: This 10-year-old Japanese boy was referred for further evaluation of a QS pattern in lead V1 and flat or inverted T waves in leads II, III, aVF, and V1 to V4. These ECG abnormalities were first detected on an ECG obtained when he was 6 years old and showed no change during the next 4 years. The boy had no family history of myocardial disease or sudden cardiac death. A chest radiograph, blood chemistry tests, and CAG showed normal results. Although 2-DE showed normal fractional shortening (0.40) and segmental wall motion, myocardial scintigraphy disclosed widespread areas of low tracer perfusion in the left ventricular wall (Fig 4). Cardiac catheterization revealed mild elevation of the left ventricular end-diastolic pressure (13 mm Hg) and mean main pulmonary arterial pressure (12 mm Hg). However, arterial pressure (113/71 mm Hg; mean, 92 mm Hg) and CI (4.5 L/min/m²) were normal. Biopsy specimens from the right ventricular apex revealed sporadic hypertrophic myocardial nuclei with marked fibrosis and mild inflammatory cell infiltration in the interstitial tissue, suggesting a history of myocarditis.

Patient 4: This 9-year-old Japanese girl was referred to us because of inverted T waves in leads II, III, and aVF. This abnormality had not been detected on a routine ECG obtained when she was 6 years old. Her family history was unremarkable. A chest radiograph and blood chemistry tests showed normal findings. 2-DE also showed normal fractional shortening (0.34) and segmental wall motion, but myocardial scintigraphy showed areas of low tracer perfusion in the apex and anterior wall. Although the

**Figure 1.** ECG recorded in patient 1. Flat or inverted T waves were recorded in leads III, aVF, and V1 to V5.
results of left ventriculography and CAG were normal, mild elevation of the left ventricular end-diastolic pressure was disclosed by cardiac catheterization. CI (4.2 L/min/m²) and aortic pressure (112/65 mm Hg; mean, 87 mm Hg) were normal. Biopsy specimens from the right ventricular apex revealed hypertrophy of myocardial nuclei with infiltrating inflammatory cells and mild fibrosis in the interstitial tissue.

**Discussion**

Routine ECG may be the only feasible strategy for identifying individuals with asymptomatic myocarditis and could help resolve the difference between the incidence of diagnosed cases of myocarditis and the incidence of cases identified histologically at autopsy.5–7 Press and Lipkind8 reported that acute myocarditis was diagnosed in 7 of approximately 60,000 patients (0.012%) seen at a pediatric emergency department for illnesses. Noren et al9 reported that histologic evidence of myocarditis was found in 4.2% of 48 children who died as a result of accidents, homicides, or suicides, and in 16.7% of 90 children who experienced sudden death. Kline et al10 also reported that histologic myocarditis was proved in 49 (2.7%) of 1,800 consecutive autopsies performed on patients < 16 years old. The results of Noren et al9 and Kline et al10 suggest that myocarditis is a major cause of sudden cardiac death in the pediatric population, and that sudden death may be the first indication of the presence of acute myocarditis. The present results suggest that the number of children at risk of sudden cardiac death because of undiagnosed asymptomatic myocarditis is greater than previously thought.11 Although we only performed histologic examinations on children with abnormal ST
or T waves, supraventricular and ventricular arrhythmia or some kinds of conduction disturbances can be the sole ECG findings of myocarditis. Therefore, a larger scale of histologic study including children with these arrhythmias might increase the incidence of diagnosed myocarditis. However, the problem in this kind of screening is that a patient with myocarditis who shows no ECG abnormality could be missed. Therefore, the present study design may be insufficient to know the real incidence of asymptomatic myocarditis because of inevitable sampling error. Because children without any ECG abnormality will have screening ECG every 3 years in this program, close attention should be paid to their ECG changes.

The analysis of 12 children with ST-T abnormalities indicates that ST depression or negative T waves in leads II, III, and aVF do not always suggest myocardial injury or ischemia, but those in lead V5 may highly suggest the existence of myocardial damage. However, to avoid missing subtle myocarditis, it appears helpful to perform 2-DE and 201Tl myocardial scintigraphy in a patient in whom ST depression or negative T waves are recorded in at least two of leads II, III, and aVF. Furthermore, judging from the results of the present studies, endomyocardial biopsies should strongly be considered when asymptomatic children present with specific ST-T wave abnormalities.

Another important suggestion from the present findings is that asymptomatic myocarditis may be, or progress to, chronic myocarditis in some patients. In most cases, acute myocarditis is self limiting, and patients recover from myocardial damage with time. However, although an accurate incidence was unknown, biopsy studies in cardiomyopathy clearly showed the existence of chronic myocarditis.12–14 Our patient 2 recovered spontaneously as indicated by ECG and histologic findings 1 year later. However, cardiac hypofunction and histologic evidence of myocarditis persisted in patient 1, and massive fibrosis was observed in patient 3, who had demonstrated a QS pattern in lead V1 and an inverted T wave on an ECG obtained 4 years earlier. The results of myocardial scintigraphy were consistent with the histologic findings in these subjects. Because CAG was normal in these children, the perfusion abnormalities detected by scintigraphy may have reflected marked myocardial degeneration or loss and fibrosis rather than myocardial infarction.15,16 The usefulness of 201Tl myocardial scintigraphy in the diagnosis of myocarditis...
acute myocarditis has been variously reported.\textsuperscript{17,18} Five of five children with histologic abnormalities showed perfusion defects in the present study, which appears unusual. However, as shown by Kawamura et al,\textsuperscript{17} \textsuperscript{20}Tl myocardial scintigraphy may coincide well with the histologic results in a pediatric population. The biopsy specimens from patients 3 and 4 showed fibrosis, infiltrating inflammatory cells, and hypertrophic myocardial nuclei, but no myocardial degeneration. These findings may not suggest acute or active myocarditis, but may suggest a history of myocarditis or idiopathic dilated cardiomyopathy. Long-term follow-up and repeat myocardial biopsy are required to make an answer to this question. Polymerase chain reaction analysis of viral genome might have provided more important and interesting information about the incidence and clinical features of asymptomatic myocarditis.

Abnormal Q waves have been observed in patients with myocarditis\textsuperscript{19,20} and have been attributed to extensive myocardial damage or loss and subsequent fibrosis. Although fibrosis may actually indicate healing, animal studies have shown that it is impossible to determine whether such fibrosis will subsequently lead to cardiac dysfunction or ventricular dysrhythmias.\textsuperscript{21} The patient in the present study with right ventricular dysplasia may originally have suffered from myocarditis, although we excluded this patient from our evaluation. Regular histologic examination of biopsy specimens and cardiac examinations, including a 24-h ambulatory ECG recording, may be helpful for predicting the clinical course.

Atrial septal defects, cardiomyopathy, QT prolongation, and various kinds of arrhythmias have been detected in schoolchildren during mass ECG screening. The present results suggest that such a screening program may also be useful for detecting asymptomatic myocarditis. Therefore, although we cannot tell whether the ECG mass screening is cost-effective or not, this program will produce more benefits in the future from detection of asymptomatic myocarditis. More extensive study is needed to obtain detailed information about the prevalence and characteristics of asymptomatic myocarditis.

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