Young Vasospastic Angina Patients Less Than 20 Years Old

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**Background:** Japanese Circulation Society (JCS) guidelines do not include adolescents with coronary artery spasm.

**Methods and Results:** We recruited 18 adolescents less than 20 years old with vasospastic angina (VSA); 11 were Japanese and 3 had chest symptoms for >12 months before admission. ST-segment elevation was observed in 11 patients and none of the 18 patients had a fixed stenosis. Spasm provocation tests were performed in 9 patients and two-thirds had multiple spasms; 6 suffered from acute myocardial infarction and ventricular fibrillation occurred in 2 patients; 1 patient died and the remaining 17 patients survived.

**Conclusions:** Clinical status of adolescents with VSA was as severe as in adults with refractory VSA. Cardiologists should cooperate with pediatricians to diagnose and treat adolescents with VSA. There is a need to establish the additional issues for adolescents with coronary spasm in the JCS guidelines.

**Key Words:** Adolescents; Cardiologists; Guidelines; Pediatricians; Vasospastic angina

Coronary artery spasm may be involved in the pathogenesis of various cardiac diseases such as sudden cardiac death, acute myocardial infarction, fatal arrhythmias, heart failure, angina pectoris, atypical chest pain and other disorders. The majority of patients with vasospastic angina (VSA) are older than 50 or 60 years, but occasionally adolescents present with VSA in the clinic. However, the particular issues of adolescent VSA are not covered by the Japanese Circulation Society (JCS) guidelines. Therefore, we recruited patients less than 20 years old with VSA and investigated their real-world data.

**Methods**

We recruited the data for 18 patients less than 20 years old with VSA reported in the PubMed database. As shown in Table 1, 11 were less than 15 years old; 10 were male and 8 were female; 11 patients were Japanese, and the other 7 patients were included 3 Americans, 1 Turk and 1 Chinese. None of the 18 patients had hypertension or diabetes mellitus/dyslipidemia. Coronary artery stenosis was not found in any of the 18 patients.

**Duration of VSA Before Admission**

Sudden onset occurred in 13 patients, who had emergency admission by ambulance, and 5 patients had a history of chest symptoms before admission; 3 patients had chest symptoms for more than 12 months. The longest duration of chest symptoms before diagnosis was 36 months.

**Chief Complaint**

Chest pain or chest oppression was the chief complaint in 12 patients and cardiopulmonary arrest was the first event in 2 patients. In 1 case the patient only had toothache without chest symptoms and another patient had dyspnea on effort without chest pain or oppression.

**Passive Smoking**

In 1 case the patient had an obvious passive smoking history because both parents had a history of smoking for more than 18 years, even at home. Another patient did not have a history of passive smoking, but we could not obtain definitive history of passive smoking for the remaining 16 patients.

**Time and Duration of Chest Pain**

Chest symptoms occurred at rest in 7 patients, 4 patients complained of chest symptoms on effort and 2 patients had chest symptoms both at rest and on effort. Chest pain occurred in the daytime in 7 patients, 3 patients complained of chest pain at nighttime, and 3 patients had chest pain attacks both day and night. The duration of chest pain was a few minutes to 3 h; 5 patients had <10 min of angina whereas 4 patients had >60 min of chest pain.

**ECG Findings on Admission**

Ischemic ECG changes were observed in 14 patients, ST-segment elevation was observed in 11 patients, and 1 patient had ST-segment depression on admission. Ischemic ECG changes in inferior leads were recognized in 6 patients, and anterolateral ischemia was found in 9 patients.

**Elevation of Cardiac Enzymes and Wall Motion Abnormality**

As shown in Table 2, elevated creatine phosphokinase (CPK)
Spasm Provocation Tests

Spasm provocation tests were performed in 9 Japanese patients, but not in the other 11 patients. Intracoronary administration of acetylcholine (ACh) provoked diffuse spasm in all 9 patients. Both right and left coronary artery spasm provocation tests were performed in 5 patients. Multiple spasms occurred in 6 of 9 patients, and 3 patients had triple vessel spasm.
Young VSA Patients

Discussion

Here we summarize the clinical data for adolescents less than 20 years old with VSA. A total of 6 patients had AMI and 1 patient died. In all 18 cases, a severe clinical state similar to refractory adulthood VSA was observed in the past. Cardiologists should cooperate with pediatricians to establish the diagnosis and treatment of adolescents with VSA.

Pitfalls of Spasm in Adolescents

If adolescent patients complain of chest pain, pediatricians and cardiologists may suspect mitral valve prolapse, myocarditis, or atypical chest pain. Although coronary artery spasm is involved in the pathogenesis of chest pain even in adolescents, we may infrequently encounter these young VSA patients. In this study, the majority of adolescents complained of chest pain or chest oppression, but cardiopulmonary arrest was the first attack in 2 adolescents, another complained just of toothache without chest symptoms and another patient had dyspnea on effort. Pediatricians and

### Table 2. Clinical Characteristics and Angiographic Findings in Patients Less Than 20 Years Old With Vasospastic Angina

| No. | Cardiac enzymes | UCG         | CAG         | ACh/ER | Spasm | Alive/dead | Medication               | Complications          |
|-----|-----------------|-------------|-------------|--------|-------|------------|--------------------------|------------------------|
| 1   | Normal          | Septal akinesia | Normal       | Not done | UC    | Alive      | Nifedipine 10 mg (3 months) | Angina-free for 14 months |
| 2   | CPK 349 IU/L    | Normal       | Normal       | Not done | UC    | Alive      | Nifedipine/isosorbide dinitrate | None                   |
| 3   | CPK 11,690 IU/L | Anterolateral akinesia | Normal       | ACh (L 100) | LAD (90)/LCX (95) | Alive | UC | AMI, VF, DC, IABP, PCPS |
| 4   | UC              | UC          | Normal       | ACh     | LAD/LCX | Alive      | UC | AMI, CPA, eNOS abnormality |
| 5   | UC              | UC          | UC          | UC     | Positive | Alive      | UC | AMI, VSA |
| 6   | CPK 905 IU/L    | Normal       | Normal       | Not done | UC    | Alive      | Verapamil 4 mg/kg | AMI, Ca-67 |
| 7   | Normal          | Anterolateral hypo LVG | Normal       | ACh (L 100) | LAD (d) | Alive | Ca unknown (20 months) | None |
| 8   | Normal          | Normal       | Normal       | Not done | UC    | Alive      | Ca/nitrate | None |
| 9   | Troponin I elevated | UC          | Normal       | Not done | UC    | Alive | UC | None |
| 10  | Normal          | LVH (apex)  | Normal       | ACh (L 50/R 50) | RCA (d)/LAD (d)/LCX (d) | Alive | Ca/vasodilator/statin | VF, DC |
| 11  | UC              | Lateral OMI on autopsy | No stenosis | Not done | UC    | Dead | None | Marked intimal hyperplasia |
| 12  | CPK/CK-MB elevated | UC          | Normal       | Not done | UC    | Alive | UC | None |
| 13  | CPK 1,815 IU/L  | Normal       | Normal       | Not done | Dilated after ISDN | Alive | UC | None |
| 14  | Troponin T positive | Normal       | Normal       | ACh (L 50/R 50) | LAD (d)/LCX (d) | Alive | Ca | AMI |
| 15  | CPK 1,050 IU/L  | Normal       | Normal       | ACh (L 50) | 8 (d) | Alive | Ca | AMI |
| 16  | CPK 407 IU/L    | Normal       | Normal       | ACh (R 50/L 100) | EC    | Alive | DiIiazem R 100 mg/nifedipine CR 20 mg | None |
| 17  | Normal          | Diffuse hypo %FS 28 | Normal       | ACh/ER/ERACH | RCA (d)/LAD (d)/LCX (d) | Alive | Decreased LV |
| 18  | CPK 408 IU/L    | Decreased EF 60% | Normal       | ACh (R 25/L 50) | RCA (d)/LAD (d)/LCX (d) | Alive | Benidipine 2 mg/isosorbide mononitrate 20 mg/nicorandil 15 mg | Decreased LV |

ACh, acetylcholine; AMI, acute myocardial infarction; Ca, calcium-channel antagonist CAG, coronary arteriography; CPA, cardiopulmonary arrest; CPK, creatinine phosphokinase; (d), diffuse spasm; DC, direct current; EF, ejection fraction; eNOS, endothelial nitric oxide synthase gene; ER, ergonovine; FS, fractional shortening; Ga, gadolinium; IABP, intra-aortic balloon pumping; L, left; LAD, left anterior descending artery; LCX, left circumflex artery; LVH, left ventricular hypertrophy; OMI, old myocardial infarction; PCPS, percutaneous cardiopulmonary support; VF, ventricular fibrillation; VSA, vasospastic angina; R, right; RCA, right coronary artery; UC, uncertain; UCG, ultracardiography.

Medications

Calcium-channel antagonists were administered to 10 patients (2 for 1 patient; 1 for 9 patients), 4 patients had another vasodilator and there was no precise description of medications for the remaining 7 patients. Nitrates were administered to 2 patients.

Complications and Prognosis

In 6 cases the patient suffered from acute myocardial infarction and ventricular fibrillation occurred in 2 patients. Direct current was necessary to recover sinus rhythm for 2 patients. As cardiopulmonary support, intra-aortic balloon pumping and percutaneous cardiopulmonary support were necessary for 1 rescue patient. Endothelial nitric oxide synthase gene abnormality was found in 1 patient (case no. 4, Table 2): T−786→C, A−922→G, and T−1468→A mutations in the 5′-flanking region on 1 allele. Overall, 1 patient died but the remaining 17 patients survived.
cardiologists should consider coronary artery spasm when an adolescent less than 20 years old complains of chest pain. Furthermore, cardiologists and pediatricians should question the adolescent’s condition precisely.

**Spasm Provocation Testing in Adolescents**
Spasm provocation tests are necessary to diagnose the presence of coronary artery spasm in the clinic. We used the dose of pharmacological agents recommended in the JCS guidelines. When we perform AcCh testing, we inject an incremental AcCh dose of 20/50/100 μg into the left coronary artery and 20/50 μg into the right coronary artery. Furthermore, the JCS guidelines recommend continuous administration of ergonovine (ER), not bolus injection. Cardiologists perform AcCh or ER testing when diagnosing adult patients with VSA, whereas pediatricians are not familiar with performing these spasm provocation tests in the clinic. Pediatricians should perform these spasm provocation tests with trained cardiologists. The optimal maximum dose of AcCh or ER in adolescents needs to be determined in order to perform the spasm provocation tests without irreversible complications.

**Medications**
Spontaneous remission is rarely observed in patients with VSA and sudden cardiac death can occur after self-cessation of medications by some with adult VSA patients. Medications including vasodilators in adolescents with coronary VSA and sudden cardiac death can occur after self-cessation of these medications. Cardiologists should corroborate with pediatricians to ensure good quality of life and excellent outcomes with VSA.

**Adolescents With Coronary Spasm in the Future**
Cardiologists and pediatricians should investigate coronary artery spasm in adolescents in the clinic, because coronary abnormal response has increased in Japanese patients, possibly with the widespread occurrence of metabolic syndrome, which has increased all over the world, even in adolescents.

Nakayama et al reported that the T→C mutation in the 5'-flanking region of the endothelial nitric oxide synthase (eNOS) gene was associated with coronary spasm. We found 1 patient with that mutation. Genetic analysis including eNOS may help diagnose adolescents with VSA in the future. Cardiologists should also campaign to protect adolescents from secondhand smoke. Furthermore, many adolescents with non-variant angina or low disease activity VSA could be present clinically, so collaboration between pediatricians and cardiologists is essential for successfully treating adolescents with VSA in Japan.

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None.

**Conflicts of Interest**
The authors declare that they have no conflicts of interest.

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