Ampulla Cardiomyopathy after Hypoglycemia in Three Young Female Patients with Anorexia Nervosa

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Abstract

Ampulla cardiomyopathy is named after the echocardiographic abnormalities occurring in this condition, characterized by extensive akinesis (ballooning) of the apical region with hypercontraction of the basal segment of the ventricle. We describe 3 young female anorexia nervosa patients showing evidence of this cardiac complication after hypoglycemia. One case was complicated by echocardiographically confirmed ampulla cardiomyopathy while the other 2 patients showed increases in myocardial enzymes and transient electrocardiographic abnormalities consistent with this complication. The precipitating event for all three patients was hypoglycemic coma, and this is the first case report in which this factor lead to the complication of ampulla cardiomyopathy in anorexia nervosa patients.

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Key words: anorexia nervosa, hypoglycemia, ampulla cardiomyopathy (Takotsubo-like cardiomyopathy), reversible myocardial dysfunction

Introduction

Anorexia nervosa (AN) is characterized by a decrease in caloric intake, weight loss, amenorrhea, and behavioral changes. In addition to abnormal laboratory findings, severe malnutrition causes myocardial dysfunction in AN patients (1), with hypotension, bradycardia, and radiographic evidence of decreased cardiac size often occurring; however left ventricle (LV) function generally remains normal (2). In AN patients with chronic malnutrition in whom LV contraction gradually decreased, focal myocardial necrosis or myocardial atrophy was evident on histopathological examination (3, 4). Major cardiovascular complications that could cause sudden death in AN patients are acute heart failure or ventricular arrhythmia due to hypokalemia or hypomagnesemia (5–7). The electrocardiographic (ECG) abnormalities associated with AN are sinus bradycardia, low voltage P waves and QRS complexes, QTc interval prolongation, non-specific ST-T changes, ST segment depression or U waves, most of which are reversible (5–11). ST-T change or T wave inversion are considered to result from stimulation of hypothalamic sympathetic centers causing release of catecholamines within the myocardium (12). Echocardiographic abnormalities in this disease consist of mitral valve prolapse (MVP), diminished LV mass, pericardial effusion, and reduced stroke volume or cardiac output (5–11).

Ampulla cardiomyopathy (Takotsubo-like cardiomyopathy) is named after echocardiographic abnormalities seen in this condition, which are characterized by extensive akinesis (ballooning) of the apical region with hypercontraction of the basal segment of the ventricle (13). Patients with ampulla cardiomyopathy demonstrate cardiac enzyme abnormalities and ECG changes similar to those seen in acute myocardial infarction, without significant luminal narrowing of the coronary arteries on angiography. Ventricular function normalizes within several weeks. The etiology of ampulla cardiomyopathy is still unclear, but it has been considered that the reversible LV asynergy with ST segment elevation could result from myocardial stunning induced by multi-vessel coronary spasm. Ampulla cardiomyopathy usually occurs after emotional stress, subarachnoid hemorrhage, pheochromocytoma, trauma, and catecholamine administration (13, 14).

We describe the case of a young female AN patient that was complicated by confirmed ampulla cardiomyopathy...
after a hypoglycemic episode and those of 2 patients who showed increases in myocardial enzymes and transient ECG abnormalities after hypoglycemia that were consistent with this complication. Our findings suggest that myocardial lesions such as those seen in ampulla cardiomyopathy could occur more frequently than currently detected.

For editorial comment, see p 171.

Case Report

Case 1

A 17-year-old woman was admitted to the Institute of Clinical Endocrinology at Tokyo Women’s Medical University Hospital Department of Medicine due to severe emaciation and malnutrition-induced liver dysfunction. The patient had suffered from restricting type AN since the age of 11, at which time her height was 137.4 cm and weight was 26.8 kg. Body weight had remained between 25 and 30 kg, and menarche had not occurred. After entering high school, further weight loss took place (from 28 to 23 kg) on a restricted diet of 600–700 kcal/day. On admission, the patient was severely emaciated, with a height of 140 cm and weight of 23 kg. Carotenosis and anemia were apparent from examination of the skin. Pulse rate was 56/min; blood pressure (BP), 84/50 mmHg; body temperature, 36.2°C; and respiratory rate, 12/min, while breath and heart sounds were normal. Generalized and severe muscle atrophy with weakness was evident and deep tendon reflexes were sluggish.

Routine laboratory studies (Table 1) revealed pancytopenia, hypoproteinemia, hypoalbuminemia, and decreased levels of rapid turnover proteins. Serum levels of transaminases were moderately increased with negative results on hepatitis B antigen and hepatitis C antibody testing. Serum levels of triiodothyronine (T3) and insulin-like growth factor were also extremely reduced. A chest roentgenogram revealed a decrease in cardiothoracic ratio to 32% but ECG was unremarkable other than showing low voltage (Fig. 1A).

On the 2nd day of admission, the complication of hypoglycemic coma developed, with blood glucose level falling to below 20 mg/dl. Full recovery of consciousness took 6 hours after intravenous administration of glucose. The patient did not experience chest pain or oppressive sensation, cold sweats, fear, or pain associated with this episode. On the 3rd day of admission, the ECG revealed sinus tachycardia with negative T wave in leads II, III, aVF, and V3–6 (Fig. 1B), with a further increase in serum CK to 342 U/l (normal range: 23–45 U/l) and a rise in CK-MB to 8.7 IU/l (normal range: <23.4 IU/l). Echocardiography demonstrated “ampulla-shaped” asynnergy, in other words, a large akinetic area around the apex and hypercontraction of the basal segments with reduction of ejection fraction (EF) to 56% (Fig. 2). These contractile findings were consistent with a diagnosis of ampulla cardiomyopathy. Myocardial scintigraphy using TI and I-123-methyl-iodo-phenyl pentadecanoic acid (BMIPP) on the 4th day demonstrated a relative deficit of BMIPP in the apical region (Fig. 3), indicating dissociation between blood flow and metabolism compatible with ampulla cardiomyopathy. Myocardial scintigraphy using I-123-metaiodobenzyl-guainidined (MIBG) on the 6th day showed a deficit in the apical lesion, indicating decreased catecholamine metabolism in this region apex, also compatible with ampulla cardiomyopathy (Fig. 4). Plasma levels of NA increased to 604 pg/ml on the 2nd day after onset and returned to normal on the 10th day after onset. LV contraction also normalized on the 10th day of onset with EF measured at 65% on echocardiography, whereas ECG changes lasted 4 months (Fig. 1C).

Case 2

A 25-year-old woman was admitted to the department of psychology due to weight loss from 39 kg to 25 kg over 3 months. She had developed restricting type AN at the age of 11, and had experienced repeated hospital admissions for ongoing weight loss occurring after having restricted her diet on entering high school. The day before admission, her family noticed drowsiness and suspected hypoglycemia. On admission, the patient was cachectic with a height of 157 cm and weight of 22.5 kg. Pulse rate was 100/min and BP was

| Table 1. Results of Routine Laboratory Investigations |
|----------------|---------|---------|---------|
|                | Case 1  | Case 2  | Case 3  |
| WBC (5,000–8,500/uL) | 1,510   | 1,630   | 6,300   |
| Hb (12–16 g/dl)     | 10.2    | 12      | 15      |
| Plt (15–35×10^12/uL) | 10.2    | 33      | 14.4    |
| TP (6.5–8.2 g/dl)   | 5.4     | 5.8     | 5.1     |
| Alb (3.8–8.2 g/dl)  | 3.5     | 4       | 3       |
| T Bil (0.1–1.0 mg/dl)| 0.4     | 0.7     | 0.7     |
| AST (11–31 IU/l)    | 486     | 330     | 680     |
| ALT (4–31 IU/l)     | 426     | 512     | 863     |
| LDH (249–438 IU/l)  | 483     | 295     | 1,458   |
| Amy (58–165 IU/l)   | 180     | 196     |         |
| CPK (36–163 IU/l)   | 174     | 549     | 1,815   |
| BUN (8–20 mg/dl)    | 25.1    | 4       | 23.4    |
| Cr (0.7–1.3 mg/dl)  | 0.38    | 0.31    | 0.77    |
| Na (135–145 mEq/l)  | 140     | 128     | 136     |
| K (3.4–4.9 mEq/l)   | 3.6     | 4.8     | 4.4     |
| Cl (98–108 mEq/l)   | 106     | 90      | 99      |
| FBS (70–100 mg/dl)  | 20>     | 33      | 20>     |
| T chol (120–219 mg/dl)| 115       | 69     | 111     |
| TG (40–149 mg/dl)   | 31      | 85      | 37      |
| T3 (0.9–1.7 ng/ml)  | 0.58    | 0.56    | 1.73    |
| IGF-1 (121–436 ng/ml)| 9.4     | 57      | 150     |


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100/74 mmHg, while breath and heart sounds were normal. The results of routine laboratory studies revealed pancytopenia, hypoproteinemia, and decreased levels of rapid turnover proteins. Serum transaminase levels were moderately increased, while those of T3 and IGF-1 were decreased (Table 1). A chest roentgenogram showed a decrease in cardiothoracic ratio to 35%. ECG demonstrated sinus tachycardia with T wave inversion in leads II, III, V5, and V6 (Fig. 5A) with an increase in serum CK to 549 IU/l. Serum catecholamine levels were elevated (NA 765 pg/ml and DA 81 pg/ml). On the 5th day of admission, the ECG normalized (Fig. 5B) and UCG did not demonstrate any abnormal LV contraction. Myocardial scintigraphy performed on the 7th and 9th day of admission failed to reveal abnormal findings.

**Case 3**

A 33-year-old woman was admitted to our hospital on an emergency basis due to hypoglycemic coma. She had developed binge eating/purging type AN at the age of 23. After marrying, the disease progressed to include self-induced vomiting and resulted in repeated hospital admissions for malnutrition or hypoglycemia. Over the 2 month-period prior to admission the patient’s weight decreased from 33 kg to 25 kg, and on admission, she was cachectic with a height of 158 cm and a weight of 24.0 kg. Pulse rate was 72/min and BP was 82/54 mmHg. She regained full consciousness following glucose infusion, but did not describe chest pain or oppressive sensation. Routine laboratory studies revealed hypoproteinemia, decreased levels of rapid turnover proteins and a moderate increase in transaminases (Table 1).

ECG showed sinus rhythm with T wave inversion in leads II, III, V1, and V5-6 (Fig. 6A). Raised serum levels of CK

Figure 1. Electrocardiographic findings on admission (A), on the 3rd day (B), and after the 4th month (C). (A) ECG was within the normal range except for generalized low voltage. (B) ECG revealed sinus tachycardia with ST segment elevation and T wave inversion in leads II, III, V5, and V6. (C) Electrocardiographic findings were normalized.

Figure 2. Echocardiography demonstrated “ampulla-shaped” asynergy; in other words, a large akinetic area around the apex and hypercontraction of the basal segments with reduction of ejection fraction (EF) to 56%.
(1,815 IU/l) and CKMB (91.9) IU/l were also evident. On the 7th day of admission, cardiac enzymes normalized and echocardiography showed recovery of LV contraction.

Myocardial scintigraphy using TI and BMIPP/MIBG failed to demonstrate abnormal deficits 1 month after admission. ECG normalized 1 month later (Fig. 6B).

Discussion

To our knowledge, this is the first report of ampulla cardiomyopathy occurring as a complication of hypoglycemic coma in anorexia nervosa. Of the present patients, a definitive diagnosis of ampulla cardiomyopathy was reached in case 1. Although neither case 2 nor case 3 exhibited the typical findings of ampulla-shaped asynergy on ultrasonic echocardiogram (UCG), their ECG changes and clinical courses strongly indicated stunned myocardium. As UCG was performed on days 5 and 7 in case 2 and 3, respectively, and ampulla-like asynergy resolves within 2–14 days in this condition (13–16), there was a possibility that UCG was performed too late to detect such abnormal findings in these patients.

No patients in this report had a past history of cardiac illness or ECG abnormalities. ECG changes appeared on the day of hypoglycemia or the following day, and normalized over a period from 5 days to 2 months after onset. Most previous reports of patients with ampulla cardiomyopathy have involved elderly females (13–16), with normal coronary arteriography indicating coronary spasm as a causative factor in some cases (13–16). Biopsy specimens revealed focal myocyte injury, suggesting that focal and disseminated myocardial damage had occurred (13–16). Most patients had a history of exposure to emotional stress or were complicated by subarachnoid hemorrhage, pheochromocytoma or trauma (13, 14). However, the precipitating event for our three patients was hypoglycemic coma, which has not previously...
been reported to have such a role and did not occur in a single report in the literature of AN complicated by ampulla cardiomyopathy.

In order to examine the pathomechanism of this complication, we investigated myocardial functional sympathetic innervation, fatty acid metabolism, and perfusion using MIBG, BMIPP, and $^{201}$TI, respectively. Radiolabeled MIBG is taken up by sympathetic nerve endings and maps functional sympathetic nerve density, whereas BMIPP evaluates myocardial long-chain fatty acid uptake, which is closely related to transiently reduced cardiac function. Myocardial perfusion did not seem to be impaired even in the acute phase, while fatty acid metabolism was depressed and the defective uptake of BMIPP was also seen in Case 1. These findings were compatible with previous reports of ampulla cardiomyopathy (13–16).

It is speculated that catecholamine hypersecretion might be the cause of stress-induced ampulla cardiomyopathy (13–16). Excessive catecholamine release couples the beta-
adrenergic receptors and depresses contraction. Furthermore, transient ventricular asynergy resembles the left ventricular asynergy induced by catecholamine crisis due to pheochromocytoma (14). In anorexia nervosa, plasma catecholamines and their metabolites are decreased (17, 18). However, in Cases 1 and 2, plasma and urinary catecholamines increased in the acute phase, possibly induced by hypoglycemia. Whether or not excess catecholamine release would induce ampulla cardiomyopathy remains unknown as there have been no reports of ampulla cardiomyopathy after hypoglycemic coma in diabetic patients. However, ECG changes have been demonstrated during insulin-induced hypoglycemia in both patients with diabetes mellitus (DM) and healthy subjects (19–22). In DM patients, ST-T changes, flattening of the T wave, T wave inversion, or QTc interval prolongation are reported to be associated with hypoglycemia, and these ECG changes normalize as blood glucose levels increase. Furthermore, cardiac enzymes were normal, and scintigraphy using TI and BMIPP did not show any filling defects. In healthy subjects, similar phenomena are reported (19–22). It is speculated that the ECG changes resulted from insulin-induced hypokalemia and catecholamine elevation, and therefore returned to normal as hypoglycemia improved. All patients described here had a long history of very poor nutrition and a severe degree of emaciation, factors which are possibly related to the occurrence of ampulla cardiomyopathy in these anorexia nervosa patients.

Hypoglycemia is not a rare event in AN patients and is often recurrent. However, since it tends to resolve rapidly, cardiac enzymes and ECG are not often evaluated. Furthermore, echocardiographic evidence of asynergy is relatively short-lived and can be hard to detect. Since the recurrence of ampulla cardiomyopathy could lead to fatal cardiac dysfunction, we believe that clinicians should have a high index of clinical suspicion for this complication.

References