Cardiac cephalalgia: a case series of four patients and updated literature review

Hitoshi Kobata*

Abstract

Background: Cardiac damage is common in patients with acute brain injury; however, little is known regarding cardiogenic-induced neurological symptoms. In the International Classification of Headache, Third Edition (ICHD-III), cardiac cephalalgia is classified as a headache caused by impaired homeostasis.

Methods: This report presents four patients with acute myocardial infarction (AMI) who presented with headache that fulfilled the ICHD-III diagnostic criteria for cardiac cephalalgia. A systematic review of cardiac cephalalgia using the Preferred Reporting Items for Systematic Reviews and Meta-analyses guidelines is also presented.

Results: Case 1: A 69-year-old man with a history of percutaneous coronary intervention (PCI) developed sudden severe occipital pain, nausea, and cold sweating. Coronary angiography (CAG) revealed occlusion of the right coronary artery (RCA). Case 2: A 66-year-old woman complained of increasing occipitalgia and chest discomfort while riding a bicycle. CAG demonstrated 99% stenosis of the left anterior descending artery. Case 3: A 54-year-old man presented with faintness, cold sweating, and occipitalgia after eating lunch. CAG detected occlusion of the RCA. Case 4: A 72-year-old man went into shock after complaining of a sudden severe headache and nausea. Vasopressors were initiated and emergency CAG was performed, which detected three-vessel disease. In all four, electrocardiography (ECG) showed ST segment elevation or depression and echocardiography revealed a left ventricular wall motion abnormality. All patients underwent PCI, which resulted in headache resolution after successful coronary reperfusion. A total of 59 cases of cardiac cephalalgia were reviewed, including the four reported here. Although the typical manifestation of cardiac cephalalgia is migraine-like pain on exertion, it may present with thunderclap headache without a trigger or chest symptoms, mimicking subarachnoid hemorrhage. ECG may not always show an abnormality. Headaches resolve after successful coronary reperfusion.

Conclusions: Cardiac cephalalgia resulting from AMI can present with or without chest discomfort and even mimic the classic thunderclap headache associated with SAH. It should be recognized as a neurological emergency and treated without delay.

Keywords: Cardiac cephalalgia, Cardiac cephalgia, Acute myocardial ischemia, Thunderclap headache, Neurological Emergency

Background

The interaction between the brain and the heart is an emerging area of clinical interest. Cardiac damage is common in patients with acute brain injury. Neurogenic stress cardiomyopathy (also known as neurogenic stunned myocardium) is widely recognized in patients with acute neurological disease [1]; however, little is known regarding cardiogenic-induced neurological...
symptoms. In 1997, Lipton et al. reported two cases of exertional headache associated with myocardial ischemia; based on these and a review of five similar previous ones, they coined the term “cardiac cephalgia” (“cardiac cephalalgia” in the current classification) [2]. In the International Classification of Headache, Third Edition (ICHD-III) [3], cardiac cephalalgia is classified as a headache caused by impaired homeostasis (Table 1). Cardiac cephalalgia is described as migraine-like headache that occurs during an episode of myocardial ischemia and is usually aggravated by exercise. The diagnosis can be challenging because cardiac cephalalgia is uncommon and the headache is not always associated with exertion; headache may occur at rest without chest symptoms [4–6]. Only a few reported cases of cardiac cephalalgia presented with sudden severe headache (thunderclap headache), which mimics subarachnoid hemorrhage (SAH) [7–10]. Both myocardial ischemia and SAH are potentially life-threatening; therefore, early recognition with appropriate treatment is critically important. Consequently, it is essential to understand the characteristics of cardiac cephalalgia as a neurological emergency and accurately diagnose it to enable appropriate intervention. This report presents four patients diagnosed with cardiac cephalalgia and reviews the relevant literature to summarize the disease characteristics and current evidence regarding the diagnosis and treatment of this uncommon clinical entity.

**Methods**

**Cases**

Since 2009, Osaka Mishima Emergency Critical Care Center has experienced four cases of headache that fulfilled the ICHD-III diagnostic criteria for cardiac cephalalgia. Characteristics of the four patients are summarized in Table 2 and briefly described below. Coronary artery lesions are described using the American Heart Association classification (Fig. 1) [11].

**Literature review**

The PubMed (National Center for Biotechnology Information, National Institutes of Health, Bethesda, MD, USA) and Scopus (Elsevier, Amsterdam, Netherlands) databases were searched in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analyses guidelines [12]. The terms "cardiac cephalalgia" OR "cardiac cephalgia" OR "headache and acute coronary syndrome" OR "headache and myocardial infarction" OR "anginal headache" were used without a publication year limitation. The references of each publication were also reviewed to find other potentially relevant reports. Only full-text English language studies were included. Duplicated patients were excluded.

**Results**

**Case presentations**

**Case 1**

A 69-year-old man with a 50-year history of smoking presented with sudden onset severe pulsatile occipitalgia during sleep. The headache was described as the worst in his life and was accompanied by nausea, cold sweating, and a five-minute episode of unconsciousness. He had a history of hypothyroidism and percutaneous coronary intervention (PCI) in the left anterior descending artery (LAD) and the right coronary artery (RCA) for angina. Electrocardiography (ECG) in the ambulance during transport to the hospital showed ST elevation in leads II and III.

He was alert on arrival complaining of severe occipitalgia but no chest pain. Blood pressure was 132/70 mm Hg...
Table 2  Patient characteristics

| Case | Age | Sex | Site | Quality   | Intensity | Onset   | Autonomic signs      | Cardiac symptoms | Trigger | ECG            | Echocardiogram findings | Coronary lesion | Therapy                  | Follow-up |
|------|-----|-----|------|----------|-----------|---------|----------------------|-------------------|---------|----------------|--------------------------|-----------------|--------------------------|-----------|
| 1    | 69  | M   | Occipital-right shoulder | Pulsatile | Severe    | Sudden  | Nausea, cold sweating | None              | None    | ST elev in II, III, aVF | Inf wall akinesis | RCA (#2) 100% | PCI (RCA)                  | Resolved  |
| 2    | 66  | F   | Occipital | NA       | Severe    | Sudden  | Cold sweating         | Chest discomfort  | Bicycle | ST elev in II, III, aVF, V1-4 | Takotsubo | LAD (#7) 99% | Heparin, PCI (LAD)             | Resolved  |
| 3    | 54  | M   | Posterior neck-occipital | Strangulation | Moderate | Gradual | Cold sweating, faintness | Chest discomfort  | Meal    | ST elev in II, III, aVF, III AV block | Inf wall akinesis | RCA (#3) 100%, LAD (#7) 90%, LCX (#13) 100% | PCI (RCA) | Resolved |
| 4    | 72  | M   | Headache | NA       | Severe    | Sudden  | Nausea, vomiting      | None              | None    | ST elev in aVR, II, III, aVF, ST dep in V2-5 | Lat, post, inf wall akinesis, ant-septal severe hypokinesis, mitral regurgitation | RCA (#3) 99%, LCX (#11) 99%, LAD (75%) | PCI (RCA), IABP, ECMO | Resolved/Died |

EGC electrocardiography, M male, F female, NA not available, elev elevation, inf inferior, lat lateral, post posterior, ant anterior, RCA right coronary artery, LAD left anterior descending artery, LCX left circumflex artery, PCI percutaneous coronary intervention, IABP intra-aortic balloon pumping, ECMO extracorporeal membranous oxygenation.
and heart rate was 57 beats per minute (bpm). Emergency head computed tomography (CT) showed no abnormalities. ECG showed ST segment elevation in leads II, III, and aVF (Fig. 2). Echocardiography revealed akinesis of the inferior wall of the left ventricle. Blood chemistry studies showed no elevation of creatine kinase–myocardial band (CKMB) concentration (0.6 ng/mL; reference range, < 3.6 ng/mL). When repeatedly asked if he had any chest symptoms, he admitted to having slight chest discomfort. Emergency coronary angiography (CAG) was subsequently performed and acute myocardial infarction (AMI) was diagnosed. The angiogram revealed occlusion of segment 2 in the RCA (Fig. 3) and 75% stenosis of segment 12 in the left circumflex artery (LCX). During PCI for the occluded RCA, he went into ventricular fibrillation (VF), which recovered to sinus rhythm after electrical defibrillation. His headache subsided after treatment and he was discharged uneventfully 11 days later.

Case 2

A 66-year-old woman with a history of rheumatoid arthritis presented with sudden occipitalgia while riding a bicycle. The pain was moderate and gradually intensified over time. While resting, she reported chest discomfort.
and cold sweating. ECG during emergency transportation to the hospital showed ST segment elevation in leads V3–V5. On arrival, she was alert and profusely sweating. Blood pressure was 90/40 mmHg and heart rate was 60 bpm. ECG showed ST segment elevation in leads II, III, aVF, and V2–V4. CKMB was normal (1.4 ng/mL) and troponin T was negative. Emergency head CT showed no intracranial hemorrhage. CT angiography disclosed a basilar–left superior cerebellar artery aneurysm 2 mm in diameter; no bleb was visualized. Magnetic resonance imaging of the brain confirmed no hemorrhage and no arterial dissection. Therefore, the aneurysm was considered unruptured. Echocardiography revealed takotsubo-like abnormal movement with an ejection fraction of 30%.

She was initially treated with intravenous heparin. Although her headache subsided soon after admission, CKMB concentration the next day was 501.1 ng/mL. She underwent CAG 15 days later after cardiac function had been restored. A 99% stenosis was found in LAD segment 7 and stents were placed. She was discharged home uneventfully. Magnetic resonance (MR) angiography of the brain nine months later showed no change in aneurysmal size or shape.

Case 3
A 54-year-old man with a 30-year history of smoking presented with faintness, cold sweating, and nausea after eating lunch, followed by strangulating occipitalgia. He was taking medications for hyperlipidemia, hypertension, and diabetes. ST segment elevation was seen in leads II and III on ECG during transportation to the hospital. Upon arrival, he complained of moderate occipitalgia but no chest pain. Blood pressure was 66/38 mmHg and heart rate was 44 bpm. ECG showed ST segment elevation in leads II, III, and aVF. Echocardiography showed hypokinesis of the inferior wall. His headache subsided while being evaluated in the emergency room. CKMB concentration was elevated (22.8 ng/mL) and troponin T was positive; therefore, AMI was diagnosed. After initiation of vasopressors and temporary pacing, emergency CAG was performed, which showed occlusion of the RCA segment 3 and LCX segment 13, as well as 90% stenosis of the LAD segment 7. PCI was performed for the RCA, which was thought to be the culprit lesion. After hemodynamic stabilization, he underwent PCI for the LAD stenosis 15 days later. The LCX was considered a chronic occlusion and was not treated. He had no further headaches after the initial PCI and he was discharged 21 days later uneventfully.

Case 4
A 72-year-old man experienced a sudden severe headache with vomiting and called an ambulance. He was a heavy smoker and had a history of hypertension and Y-graft placement for an abdominal aortic aneurysm. When the emergency team arrived 10 min later, he was disoriented and incontinent of feces and urine. He did not complain of any chest symptoms. No obvious ST segment changes were noted on ECG during transportation to the hospital. On arrival, blood pressure was 106/82 mmHg and heart rate was 64 bpm. He vomited
and was intubated to secure the airway. ECG showed ST segment depression in leads I–III, aVF, and V2–V5 and ST elevation in aVR (Fig. 4). Echocardiography showed mitral regurgitation, akinesis of the posterior wall of the left ventricle, and hypokinesis in the anterior septum.

SAH associated with neurogenic stunned myocardium was suspected and head CT was immediately performed; no significant lesions were found. CT angiography showed no cerebrovascular abnormalities. CKMB concentration was normal (1.6 ng/mL) but troponin T was positive. His blood pressure declined to 50 mm Hg/unmeasurable after CT and heart rate declined to 30 bpm. After vasopressor support was initiated, emergency CAG was performed and revealed 99% stenosis of the RCA segment 3, 75% stenosis of the LAD segment 6, and 90% stenosis of the LCX segments 11 and 13. The patient underwent PCI for segment 3, which was considered the culprit lesion (Fig. 5). Then, an intra-aortic balloon pump (IABP) was placed and he was transferred to the cardiovascular department as a potential candidate for mitral valve replacement. He underwent veno-arterial extracorporeal membranous oxygenation and the IABP was later replaced with a catheter-based miniaturized ventricular assist device. He did not complain of headache upon awakening but died 38 days later due to hemorrhagic complications.

**Literature review**
The literature search initially identified 721 potentially relevant articles. Forty-eight articles including 55 cases of cardiac cephalalgia met criteria (Supplementary File 1). After including the four patients reported here, a total of 59 cardiac cephalalgia cases were finally reviewed. Individual patient characteristics are shown in Table 3 [13–54] and summarized in Table 4.

Cardiac cephalalgia generally occurs in middle-aged or older individuals (median age, 64 years) with male predominance (62.7%). Forty-seven patients (79.7%) were age 50 or older. Pain is typically triggered by varying degrees of exertion, sexual activity, and motion fluctuation (49.2%) but may develop at rest without any particular trigger (27.1%). Headache may occur suddenly or

![Fig. 4 Electrocardiogram of case 4 shows ST segment depression in leads I–III, aVF, and V2–V5 and ST elevation in aVR](image-url)
gradually increase in intensity. The most common location of the pain is the occipital region (39.0%), but it can occur in a variety of sites, most often bilaterally (39.0%).

The nature of the headache varies, which has been described as pulsating, throbbing, oppressive, bursting, or explosive. Regardless, the intensity is usually severe. Headaches are frequently associated with autonomic signs such as nausea, vomiting, and sweating. More than half of patients (55.9%) do not complain of chest symptoms, which makes diagnosis challenging. The reported duration of headache ranges from 30 s to a few days and they may occur intermittently for several years. Exertional headaches are almost always relieved by rest. SAH is suspected in cases of sudden severe headache and several patients underwent diagnostic lumbar puncture [2, 7–9, 24, 33, 39, 44].

ECG revealed ST segment elevation (39.0%), ST segment depression at rest (15.2%) or during stress testing (23.7%), and other abnormal findings (8.5%). ECG was normal or equivocal in four (6.8%). Among the 25 patients who underwent cardiac enzyme testing, the concentration was elevated in 21 patients (84%) and normal in four (16%).

Coronary risk factors were common: hypertension, smoking, hyperlipidemia, diabetes, and obesity were reported in 35.6%, 33.9%, 32.2%, 23.7%, and 6.8% of patients, respectively. Three patients, including one reported above, had a history of myocardial infarction or coronary intervention [28, 31]. These histories provide invaluable diagnostic clues.

Underlying cardiac pathology was AMI (50.8%), angina (47.5%), cardiomyopathy (1.7%), and not described (1.7%). CAG results were described in 51 patients. Coronary occlusion or severe stenosis was present in almost all patients. The number of affected arteries was three in 19 patients, two in 11, and one in 17; spasm was reported in two and findings were normal in two others.

PCI was performed in 26 patients and coronary artery bypass graft (CABG) in 12. Nitrates were administered in 15 patients, heparin in one, and warfarin in one. Advanced life support was performed in one patient because of cardiac arrest. Headaches resolved with improvement in myocardial ischemia. Nitroderivatives are effective and PCI or CABG leads to permanent resolution of the headache. Headache recurrence has been reported with restenosis of coronary arteries [21, 43, 46]. Overall, reported outcomes were as follows: headache resolution, 51; death, 6; not reported, 2. Three patients died of cardiac failure or its complications, including one patient reported above [18, 52]. Two others died of VF [18, 25]. One died suddenly 6 months after headache onset [28].

**Discussion**

This report presents four cases of cardiac cephalalgia that resulted from AMI. Two patients (cases 2 and 3) reported chest discomfort with associated triggers. In contrast, the other two (cases 1 and 4) presented with sudden severe headache that met the diagnostic criteria for a thunderclap headache without an identifiable trigger. The latter two lost consciousness after the headache and had no cardiac symptoms; therefore, SAH was initially suspected. After head CT confirmed no intracranial hemorrhage, emergency CAG was performed, followed by PCI. Notably, three patients presented with low blood pressure and one developed VF. Because all four exhibited abnormal findings on ECG and echocardiography, the diagnosis of cardiac cephalalgia was straightforward.

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**Fig. 5** A Right coronary angiography of case 4 shows 99% stenosis of the right coronary artery segment 3. B Left coronary angiography shows 75% stenosis of the LAD segment 6 and 90% stenosis of the LCX segments 11 and 13. C Right coronary angiography after percutaneous coronary intervention with stenting to segment 3
### Table 3  Reported cases of cardiac cephalalgia

| Author       | Year | Age | Sex | Site                  | Quality                      | Intensity | Onset       | Duration     | Autonomic signs                      | Cardiac symptoms                  | Trigger                      | ECG                     | Coronary lesion | Therapy | Follow-up |
|--------------|------|-----|-----|-----------------------|------------------------------|-----------|-------------|--------------|-----------------------------|-------------------------------|-----------------------------|----------------|-------------|-----------|-----------|-----------|
| Caskey [13]  | 1978 | 47  | M   | Right eye             | Pressing                     | Severe    | NA          | 30–40 s      | None                        | Chest pain, left arm pain    | Rest, mild exercise           | ST elevation | NA         | Nitrate   | Resolved  |
| Lefkowitz [14]| 1982 | 62  | M   | Bregmatic             | Explosive                    | Severe    | NA          | NA           | None                        | Retrosternal pain, arm numbness | ST depression (stress)        | ST elevation | NA         | RCA       | Resolved  |
| Fleetcroft [15]| 1985 | 78  | F   | Frontal               | NA                           | NA        | NA          | NA           | None                        | None                          | Vigorous exercise             | ST depression (stress)        | NA         | Nitrates   | Resolved  |
| Blacky [16]   | 1987 | 40  | M   | Bitemporal            | NA                           | NA        | NA          | NA           | None                        | None                          | Exertion                     | Nitrates (stress)            | NA         | Resolved   |           |
| Vernay [17]   | 1989 | 71  | M   | Occipital, parietal   | NA                           | NA        | NA          | NA           | None                        | Shoulder pain radiating to arms | ST depression (stress)        | NA         | Nitrates   | Resolved  |
| Takayanagi [18]| 1990 | 67  | M   | Occipital             | Pulsating                    | Severe    | NA          | a few minutes | None                        | None                          | Chest pressure               | ST elevation | NA         | Nitrate   | Died      |
| Takayanagi [18]| 1990 | 64  | F   | NA                    | NA                           | NA        | NA          | NA           | None                        | None                          | None                        | ST elevation | 3 vessel   | Nitrate   | Died      |
| Bowen [19]    | 1993 | 59  | M   | Bitemporal            | NA                           | Severe    | Sudden     | 10–30 m      | None                        | Chest pressure, left arm pain | Rest                        | ST depression (stress)        | RCA, OM     | PCI       | Resolved  |
| Ishida [20]   | 1996 | 64  | M   | Occipital             | Throbbing                    | Severe    | Sudden     | 10 h         | Nausea                      | None                          | Abdominal or chest pain       | ST depression (stress)        | 3 vessel    | PCI       | Resolved  |
| Lipton [2]    | 1997 | 57  | M   | Vertex                | Sharp or shooting            | Severe    | Gradual    | Minutes-hours | Nausea                      | Vigorous exercise, sexual activity | ST depression (stress)        | 3 vessel    | CAGB      | Resolved  |
| Lipton [2]    | 1997 | 67  | M   | Bifrontal             | Squeezty, steadily, pressing | Severe    | Gradual    | Minutes-hours | None                        | Vigorous exercise             | ST depression (stress)        | 3 vessel    | PCI       | Resolved  |
| Grace [21]    | 1997 | 59  | M   | Vertex occipital      | Bursting                     | Severe    | Sudden     | Seconds       | None                        | None                          | Mild exercise                | ST depression (stress)        | LAD, RCA    | CAGB      | Relapse   |
| Lance [22]    | 1998 | 62  | M   | Right frontal         | NA                           | NA        | Gradual    | Minutes       | None                        | Chest pain                    | Mild exercise                | ST depression (stress)        | LAD, RCA    | CAGB      | Resolved  |
| Lanza [23]    | 2000 | 68  | M   | Occipital             | NA                           | NA        | NA         | NA           | None                        | Shoulder pain                 | Rest                         | Peaked T in V2-4             | 3 vessel    | CAGB      | Resolved  |
| Lanza [23]    | 2000 | 70  | M   | Occipital             | NA                           | NA        | NA         | NA           | None                        | None                          | Rest                         | NA           | 3 vessel   | NA        | NA        |
| Amendo [24]   | 2001 | 78  | F   | Bitemporal            | NA                           | Severe    | Hours      | Vomiting     | None                        | None                          | ST elevation                | NA           | 3 vessel   | CAGB      | Resolved  |
| Author          | Year | Age | Sex | Site                      | Quality     | Intensity | Onset   | Duration | Autonomic signs | Cardiac symptoms | Trigger               | ECG                       | Coronary lesion | Therapy        | Follow-up       |
|----------------|------|-----|-----|---------------------------|-------------|-----------|---------|----------|----------------|-------------------|----------------------|------------------------|---------------------|----------------|---------------|
| Amendo [24]    | 2001 | 77  | F    | Right frontal and maxillary | NA          | Severe    | Acute   | Hours    | None           | None              | None                 | Precordial R progression | Normal         | NA            | NA            |
| Auer [25]      | 2001 | 47  | M    | Occipital                 | NA          | NA        | NA      | Minutes–2 h | NA             | NA                 | ST elevation         | LAD, RCA           | Advanced life support | Died            |
| Rambihar [26]  | 2001 | 65  | F    | Occipital                 | NA          | NA        | NA      | NA       | Shoulder and left arm pain | Exercise, meal      | ST depression (stress) | 3 vessel CABG | Partially resolved |
| Famularo [27]  | 2002 | 70  | M    | Frontoparietal bilateral  | Sharp or shooting | Severe | NA      | 2 d      | None           | Mid epigastric pain | NA                  | ST elevation | NA            | Nitrates       | Resolved        |
| Gutierrez-Morlote [28] | 2002 | 59  | M    | Vertex occipital bilateral | Dull and throbbing | Moderate-severe | Rapidly progressive | 1 d | Nausea, photophobia | Chest pain | Rest | ST depression | NA            | Nitrates       | Resolved       |
| Martinez [29]  | 2002 | 68  | F    | Left hemi-cranial          | Shooting    | Severe    | Gradual | 1 h      | None           | None              | None                 | Mild exercise, exertion | ST elevation | 3 vessel PCI | Resolved       |
| Sathirapanya [30] | 2004 | 58  | M    | Left occipital            | Sharp or shooting | Severe | NA      | 15–20 m | None           | Chest tightness | Exertion | ST elevation | 3 vessel CABG | Resolved       |
| Chen [31]      | 2004 | 76  | M    | Bitemporal                | Non-throbbing | Mild-severe | NA      | 5 m      | None           | Chest pain | Rest, exertion | ST depression (stress) | LAD, RCA | Nitrates       | Resolved       |
| Gutierrez-Morlote [32] | 2005 | 74  | F    | Bitemporal                | Pulsating   | Severe    | NA      | Minutes–hours | Nausea          | Chest tightness | Rest | ST depression | NA            | Nitrates       | Resolved       |
| Gutierrez-Morlote [32] | 2005 | 64  | F    | Uni-or bilateral          | Oppressive   | Severe    | Sudden | 1 h      | None           | None              | Rest, mild exercise | NA                  | NA            | NA            | Died after resolution |
| Korantzopoulos [33] | 2005 | 73  | F    | Occipital                 | Sharp        | Severe    | Sudden | 1 h      | Nausea, vomiting | None              | Rest | ST depression | LAD            | Nitrates       | Resolved       |
| Cutter [34]    | 2006 | 55  | M    | Biparietal                | Non-throbbing | NA      | Gradual | Minutes | None           | None              | Mild exercise, sexual activity | Normal | LAD, RCA | PCI | Resolved       |
| Seow [7]       | 2007 | 35  | M    | NA                         | Explosive    | Severe    | Gradual | 1 d      | Vomiting, cold sweating | None              | None | ST elevation | LAD            | NA            | Resolved       |
| Broner [8]     | 2007 | 72  | F    | Occipital                  | Sharp and throbbing | Severe    | Sudden | Hours | Nausea, vomiting | None | None | ST elevation | RCA            | Heparin       | Resolved       |
| Wei [35]       | 2008 | 36  | M    | Vertex to occipital bilateral | Dull        | Severe    | Rapidly progressive | NA | NA | ST elevation | LAD            | PCI | Resolved       |
| Author          | Year | Age | Sex | Site                       | Quality | Intensity | Onset   | Duration | Autonomic signs                     | Cardiac symptoms             | Trigger | ECG         | Coronary lesion | Therapy | Follow-up |
|-----------------|------|-----|-----|----------------------------|---------|-----------|---------|----------|-------------------------------------|-----------------------------|----------|-------------|-----------------|---------|------------|
| Wei [35]        | 2008 | 85  | F   | Right eye                  | NA      | NA        | NA      | NA       | NA                                 | Chest pain                 | Exercise | NA          | ST elevation   | PCI     | Resolved   |
| Wang [36]       | 2008 | 81  | F   | NA                          | NA      | Severe    | NA      | Hours    | Dizziness, diaphoresis, nausea     | VF                           | NA       | RCX         | PCI             | Resolved |
| Dalzell [9]     | 2009 | 44  | F   | Occipital                  | NA      | Severe    | Sudden  | NA       | Nausea, vomiting, sweating         | None                        | NA       | ST elevation| PCI             | Resolved |
| Sendovski [10]  | 2009 | 61  | F   | Forehead                   | NA      | Severe    | NA      | NA       | None                                | ST elevation               | None     | 3 vessel    | PCI             | Resolved |
| Chatzizisis [37]| 2010 | 42  | M   | Frontal, bitemporal        | NA      | Severe    | Sudden  | Hours    | None                                | None                        | None     | LAD         | PCI             | Resolved |
| Cheng [38]      | 2010 | 52  | F   | Throbbing                  | NA      | Severe    | Sudden  | 3 d      | None                                | Chest pain                 | Exertion | ST depression| Normal          | PCI     | Resolved   |
| Cheng [38]      | 2010 | 67  | F   | Jaw, mandible, bilateral temporal | NA      | Severe    | Sudden  | 5 m      | None                                | Exertional dyspnea          | None     | ST depression| Normal          | PCI     | Resolved   |
| Yang [39]       | 2010 | 44  | F   | Bifrontal                  | NA      | Severe    | NA      | NA       | Nausea                              | Chest tightness            | Exertion | ST depression (stress) | Nitrates, CABG | Resolved |
| Costopoulos [40]| 2011 | 55  | M   | Occipital                  | NA      | NA        | NA      | NA       | None                                | None                        | None     | Q wave      | PCI             | Resolved |
| Elgharably [41] | 2013 | 55  | M   | Frontal                    | NA      | Severe    | NA      | > 12 h   | None                                | None                        | None     | LAD         | PCI             | Resolved |
| Asvestas [42]   | 2014 | 86  | M   | Occipital                  | NA      | Severe    | NA      | NA       | None                                | None                        | None     | LCX, LAD    | PCI             | Resolved |
| Wassef [43]     | 2014 | 44  | M   | Oppressive                 | NA      | NA        | Severe  | NA       | None                                | Chest discomfort           | Exertion | LAD         | PCI             | Resolved |
| Mathew [44]     | 2015 | 47  | M   | Bioccipital, to vertex     | NA      | Severe    | NA      | A few minutes | None                          | None                        | Exertion | NA         | LAD, PCI        | Resolved |
| Prakash [45]    | 2015 | 67  | M   | Posterior to holoccephalic | Intense, excruciating | Severe | Sudden | 10–60 m | None | Lifting heavy objects, sexual activities | None | None | ST depression (stress) | CABG | Resolved |
| Chowdhury [46]  | 2015 | 51  | M   | Pre-auricular to forehead, vertex, occipital | NA | NA | NA | 2–3 m | Mild chest tightness and sweating | None | Mild ST-T change | LAD, LCX | PCI | Resolved |
| Asvestas [42]   | 2014 | 86  | M   | Occipital                  | NA      | Severe    | NA      | NA       | None                                | None                        | None     | LCX, LAD    | PCI             | Resolved |
| Mathew [44]     | 2015 | 47  | M   | Bioccipital, to vertex     | NA      | Severe    | NA      | A few minutes | None                          | None                        | Exertion | NA         | LAD, PCI        | Resolved |
| Prakash [45]    | 2015 | 67  | M   | Posterior to holoccephalic | Intense, excruciating | Severe | Sudden | 10–60 m | None | Lifting heavy objects, sexual activities | None | None | ST depression (stress) | CABG | Resolved |
| Chowdhury [46]  | 2015 | 51  | M   | Pre-auricular to forehead, vertex, occipital | NA | NA | NA | 2–3 m | Mild chest tightness and sweating | None | Mild ST-T change | LAD, LCX | PCI | Resolved |

Note: Table 3 (continued)

Author: Wei [35], Wang [36], Dalzell [9], Sendovski [10], Chatzizisis [37], Cheng [38], Cheng [38], Yang [39], Costopoulos [40], Elgharably [41], Asvestas [42], Wassef [43], Mathew [44], Prakash [45], Chowdhury [46].

Site: Right eye, NA, Occipital, Forehead, Occipital, Jaw, mandible, bilateral temporoparietal, Bifrontal, Occipital, Frontal, Occipital, NA, Oppressive, Bioccipital, to vertex, NA, Pre-auricular to forehead, vertex, occipital.

Quality: Right eye, NA, Occipital, Forehead, Occipital, Jaw, mandible, bilateral temporoparietal, Bifrontal, Occipital, Frontal, Occipital, NA, Oppressive, Bioccipital, to vertex, NA, Pre-auricular to forehead, vertex, occipital.

Intensity: NA, Severe, NA, Severe, Sudden, Severe, Sudden, Severe, Sudden, Oppressive, Severe, to vertex, NA, NA, NA.

Onset: NA, Hours, NA, Hours, Sudden, Sudden, Sudden, Sudden, A few minutes, NA.

Duration: NA, Hours, None, Hours, Sudden, 3 d, Sudden, 5 m, 2–3 m.

Autonomic signs: NA, Dizziness, diaphoresis, nausea, Nausea, vomiting, sweating, Nausea, vomiting, sweating, Nausea, Nausea, Chest tightness and sweating.

Cardiac symptoms: Chest pain, VF, None, None, None, None, Local anesthesia, None, None, None.

Trigger: Exercise, NA, Exertion, NA, NA, Exertion, Local anesthesia, Exertion, Exertion, None.

ECG: Normal, ST elevation, NA, NA, NA, SA, None, Normal, Mild ST-T change, Mild ST-T change.

Coronary lesion: NA, PCI, PCI, ST depression, PCI, PCI, PCI, PCI, PCI, PCI.

Therapy: PCI, Normal, Nitrates, PCI, PCI, PCI, PCI, PCI, PCI, PCI.

Follow-up: Resolved, Resolved, Resolved, Resolved, Resolved, Resolved, Resolved, Resolved, Resolved, Resolved.
Table 3 (continued)

| Author     | Year | Age | Sex | Site                  | Quality            | Intensity | Onset      | Duration | Autonomic signs | Cardiac symptoms | Trigger            | ECG               | Coronary lesion | Therapy   | Follow-up |
|------------|------|-----|-----|-----------------------|--------------------|-----------|------------|----------|----------------|------------------|--------------------|------------------|----------------|-----------|----------|
| Huang [47] | 2016 | 70  | F   | Bilateral posterior nuchal | Dull squeezing     | NA         | Sudden     | NA       | Dizziness      | None             | None               | ST elevation      | LAD            | PCI       | Resolved |
| Shankar [48]| 2016 | 73  | M   | Generalized           | Dull               | NA         | NA         | 5 m      | None           | None             | None               | ST depression (stress) | 3 vessel PCI    | CABG     | Resolved |
| Wang [6]   | 2017 | 40  | M   | Bitemporal            | Pulsatile, tight | Moderate-severe | NA       | 5–10 m  | Cold sweating | Chest discomfort, palpitations, sexual activities | Exertion           | Inverted T | LAD, RCA, LCX, D | PCI     | Resolved |
| Majumder [49]| 2017 | 48  | F   | NA                   | NA                 | Severe     | NA         | Hours    | None           | None             | None               | ST depression     | LAD, RCA       | PCI       | Resolved |
| Lazari [50] | 2019 | 64  | M   | Generalized          | Compressing        | Severe     | Rapidly progressive | 5–15 m  | None           | None             | None               | ST elevation      | RCA            | PCI       | Resolved |
| MacIsaac [51]| 2019 | 86  | M   | Bilateral, posterior | Dull               | Severe     | Progressive | 30–90 m  | None           | Chest pain       | None               | ST depression     | RCA, LCX, D    | Warfarin  | Resolved |
| Santos [52] | 2019 | 62  | M   | Holocranial          | Aching             | NA         | NA         | NA       | None           | Chest pain       | None               | Exertion          | Normal         | 3 vessel CABG | Died     |
| Ruiz Ortiz [53]| 2020 | 74  | F   | Vertex, Bitemporal   | Oppressive         | Moderate   | NA         | NA       | None           | Chest pain       | None               | ST elevation      | 3 vessel PCI   | PCI       | Resolved |
| Sun [54]   | 2021 | 83  | F   | NA                   | Migraine-like      | NA         | NA         | Hours    | None           | Chest pain       | None               | ST elevation     | RCA            | PCI       | Resolved |
| Kobata     | 2021 | 69  | M   | Occipital            | Pulsatile          | Severe     | Sudden     | NA       | Nausea, sweating | None             | None               | ST elevation     | RCA            | PCI       | Resolved |
| Kobata     | 2021 | 66  | F   | Occipital            | NA                 | Severe     | Sudden     | NA       | Cold sweating | Chest discomfort | Exertion           | ST elevation     | LAD            | PCI       | Resolved |
| Kobata     | 2021 | 54  | M   | Occipital            | Strangulation      | Moderate   | Gradual    | NA       | Cold sweating | Chest discomfort | Meal               | ST elevation     | 3 vessel PCI   | PCI       | Resolved |
| Kobata     | 2021 | 72  | M   | NA                   | NA                 | Severe     | Sudden     | NA       | Nausea, vomiting | None             | None               | ST elevation     | 3 vessel PCI   | PCI       | Resolved/Died |

M male, F female, NA not available, s second, m minute, h hours, d day, LAD left anterior descending artery, RCA right coronary artery, CX circumflex artery, OM obtuse marginal artery, D diagonal artery, CARG coronary artery bypass graft, PCI percutaneous coronary intervention.
Early cooperation with cardiologists enabled prompt cardiovascular examination and treatment. The headache resolved after successful coronary reperfusion in all cases.

In a study of 1546 AMI patients, headache was present (along with other symptoms) in 5.2% and was the primary complaint in 3.4% [55]. Differentiation of cardiac cephalalgia from migraine without aura has been emphasized in patients without chest symptoms. Vasoconstrictor medications (e.g., triptans, ergots) are contraindicated in patients with ischemic heart disease, while migraine-like headache may be triggered by angina treatments such as nitroglycerine [3].

The typical manifestation of cardiac cephalalgia is migraine-like pain on exertion. However, it may present as a thunderclap headache without a trigger, although this is not common. In a systemic review of thunderclap headache, more than 100 different causes were reported; cardiac cephalalgia was highlighted as an important causative systemic condition [56]. Above all, SAH is the most common cause of secondary thunderclap headache and should be the focus of initial assessment given its significant morbidity and mortality [57].

Early differentiation of SAH and AMI is crucial because both are potentially life-threatening. Rapid diagnosis and appropriate treatment are therefore critical. Because cardiac cephalalgia is not always associated with chest symptoms or ECG abnormalities, the diagnosis should be considered in middle-aged or older patients with coronary risk factors presenting with a first-episode headache. Confusingly, SAH patients can also present with cardiac symptoms. ECG abnormalities are common in these patients and left ventricular wall motion abnormalities may develop in the absence of organic coronary artery stenosis. Echocardiography may show takotsubo-like or other types of abnormal wall motion. This manifestation is transient and has been called neurogenic stunned myocardium [58], which is often associated with hypotension and elevated myocardial enzyme concentration [59]. Accordingly, hypotension, ECG abnormalities, abnormal cardiac wall motion, and mildly elevated cardiac enzyme concentration do not preclude SAH. For patients with thunderclap headache, emergency head CT is indispensable; if no significant findings are detected, a cardiac workup should be initiated. ECG, echocardiography, measurement of cardiac enzyme concentrations, and coronary artery evaluation should be performed when cardiac cephalalgia is suspected.

Several mechanisms to explain the headache induced by myocardial ischemia have been hypothesized: 1) referred pain through the convergence of vagal afferents from the heart with trigeminal neurons in the spinal trigeminal nucleus or somatic afferents from C1–C3 in the upper spinothalamic tract [2, 4, 60]; 2) elevated

| Characteristics | Variable (N = 59) |
|------------------|------------------|
| Age              | Years (median, quartile) 64 (54–72) |
| Sex              | Male 37 (62.7) |
| Trigger          | Exertion 26 (44.1) |
|                  | Other than exertion 3 (5.1) |
|                  | None 16 (27.1) |
|                  | NA 14 (23.7) |
| Onset            | Sudden 15 (25.4) |
|                  | Progressive or gradual 11 (18.6) |
|                  | NA 33 (55.9) |
| Side             | Right 4 (6.8) |
|                  | Left 2 (3.4) |
|                  | Bilateral 23 (39.0) |
|                  | NA 30 (50.8) |
| Regions          | Frontal 10 (16.9) |
|                  | Temporal 7 (11.9) |
|                  | Parietal 3 (5.1) |
|                  | Occipital 23 (39.0) |
|                  | Whole 6 (10.2) |
|                  | Eye 2 (3.4) |
|                  | NA 8 (13.6) |
| Intensity        | Severe 37 (62.7) |
|                  | Moderate-severe 2 (3.4) |
|                  | Moderate 2 (3.4) |
|                  | Mild-severe 1 (1.7) |
|                  | NA 17 (28.8) |
| Chest symptom    | Present 24 (40.7) |
|                  | Absent 33 (55.9) |
|                  | NA 2 (3.4) |
| Associated symptoms | Nausea 10 (16.9) |
|                  | Sweating 7 (11.9) |
|                  | Vomiting 5 (8.5) |
|                  | Dizziness 2 (3.4) |
|                  | Miscellaneous 5 (8.5) |
|                  | None 1 (2.0) |
|                  | NA 8 (13.5) |
| ECG              | ST elevation 23 (39.0) |
|                  | ST depression 9 (15.2) |
|                  | ST depression in stress 14 (23.7) |
|                  | Other changes 5 (8.5) |
|                  | Normal 4 (6.8) |
|                  | NA 4 (6.8) |
| Risk factors     | Hypertension 21 (35.6) |
|                  | Diabetes 14 (23.7) |
|                  | Hyperlipidemia 19 (32.2) |
|                  | Smoking 20 (33.9) |
|                  | Obesity 4 (6.8) |

Characteristics are shown as number (%) except for age
NA, not available
The vertex in the original description was classified as parietal
intracranial pressure because of venous stasis resulting from ischemia-induced ventricular hypofunction and reduced cardiac output [2, 4]; 3) vasodilation within the brain secondary to myocardial ischemia-induced release of serotonin, bradykinin, histamine, and substance P [2, 4]; 4) presence of vasospasm in both coronary and cerebral arteries [4]; and 5) reversible contraction of microvessels or cortical spreading depolarization induced by cerebral hypoperfusion [6]. The last hypothesis is based on confirmation of cerebral hypoperfusion during a headache attack in the presence of normal cerebral arteries on MR angiography [6]. CT angiography and MR angiography in the patients reported here did not reveal constriction of visible cerebral arteries either.

Headache in cardiac cephalalgia does not present with uniform clinical characteristics. Some patients visit the outpatient clinic complaining of recurrent exertional headaches, while others are brought to the emergency room in shock or a comatose state. Cardiac symptoms may be absent and ECG may be normal, even with standard stress testing [34]. To diagnose cardiac cephalalgia, clinicians must be aware of it and also suspect its presence. Interestingly, among the 48 articles reporting cardiac cephalalgia, 28 were published in neurology journals and 17 in cardiovascular journals. This may reflect the fact that patients are usually initially seen by neurologists. Overlooked or delayed diagnosis can lead to serious consequences. First-line health care professionals should be aware of cardiac cephalalgia. When it is suspected, early collaboration with cardiologists is warranted.

Conclusion
Cardiac cephalalgia resulting from AMI can present with or without chest discomfort and even mimic the classic thunderclap headache associated with SAH. It should be recognized as an emergency and treated without delay.

Abbreviations
ICH-D-III: International Classification of Headache, Third Edition; SAH: Subarachnoid hemorrhage; PCI: Percutaneous coronary intervention; LAD: Left anterior descending artery; RCA: Right coronary artery; ECG: Electrocardiography; CT: Computed tomography; CKMB: Creatine kinase–myocardial band; CAG: Coronary angiography; AMI: Acute myocardial infarction; LCX: Left circumflex artery; VF: Ventricular fibrillation; MR: Magnetic resonance; IABP: Intra-aortic balloon pump; CABG: Coronary artery bypass graft.

Supplementary Information
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Authors’ contributions
HK: study concept and design, acquisition of data, analysis, and interpretation, drafting the manuscript. The author read and approved the final manuscript.

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Availability of data and materials
The datasets used and analyzed during the current study are available from the corresponding author on reasonable request.

Declarations
Ethics approval and consent to participate
The study was approved by the Ethics Committee of the Osaka Mishima Emergency Critical Care Center. The author certifies that the study was performed in accordance with the ethical standards as laid down in the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards.

Consent for publication
Written informed consent was received from all participants for the publication.

Competing interests
The author declares that there are no competing interests.

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