Sudden cardiac arrest in a patient with epilepsy induced by chronic inflammation on the cerebral surface

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Abstract

The present study analyzed a patient with epilepsy due to chronic inflammation on the cerebral surface. The patient underwent sudden cardiac arrest. Paradoxical brain discharge, which occurred prior to epileptic seizures, induced a sudden cardiac arrest. However, when the focal brain pressure was relieved, cardiac arrest disappeared. A 27-year-old male patient underwent pre-surgical video-electroencephalogram monitoring for 160 hours. During monitoring, secondary tonic-clonic seizures occurred five times. A burst of paradoxical brain discharges occurred at 2-19 seconds (mean 8 seconds) prior to epileptic seizures. After 2-3 seconds, sudden cardiac arrest occurred and lasted for 12-22 seconds (average 16 seconds). The heart rate subsequently returned to a normal rate. Results revealed arachnoid pachymenia and adhesions, as well as mucus on the focal cerebral surface, combined with poor circulation and increased pressure. Intracranial electrodes were placed using surgical methods. Following removal of the arachnoid adhesions and mucus on the local cerebral surface, paradoxical brain discharge and epileptic seizures occurred three times, but sudden cardiac arrest was not recorded during 150-hour monitoring. Post-surgical histological examination indicated meningitis. Experimental findings suggested that paradoxical brain discharge led to cardiac arrest instead of epileptic seizures; the insult was associated with chronic inflammation on the cerebral surface, which subsequently led to hypertension and poor blood circulation in focal cerebral areas.

Key Words: chronic inflammation; epilepsy; sudden cardiac arrest; sudden death; video-electroencephalogram

INTRODUCTION

In 1902, Spratling introduced the concept of sudden unexplained death in epilepsy. Over the past 100 years, numerous studies have focused on sudden unexplained death in epilepsy. Although the mechanisms underlying sudden unexplained death in epilepsy remain poorly understood, results have demonstrated that the death is associated with epileptic seizures, in particular primary and secondary generalized tonic-clonic seizures[1-2]. There is little evidence indicating that chronic inflammation on the brain surface leads to epilepsy, or paradoxical brain discharge, which occurs prior to epileptic attack, induces sudden cardiac arrest. The present study reports an epilepsy patient with induced sudden cardiac arrest.

CASE REPORT

Clinical data

A 27-year-old, single, male college student from China was enrolled in the present study. At 16 years of age, he suddenly fell to the ground in class and was unconscious. Following this onset, he experienced general weakness, headache, and mild nausea, but was not treated at the time. One month later, these symptoms occurred again during sleep. Head CT results were negative. The patient was diagnosed with epilepsy (classification unknown), and sodium valproate (0.6 g per day) was administered. Nine months later, the patient suffered from a cold and once again experienced epileptic seizures. The dose of sodium valproate was increased to 1.2 g per day, but the epileptic seizures were not completely controlled. Secondary generalized tonic-clonic seizures occurred 5-6 times each year and mostly at night. In the past 3 years, in addition to secondary generalized tonic-clonic seizures, the patient experienced seizures in which his mind suddenly went completely blank combined with general weakness; the patient knelt on or fell to the ground, but did not exhibit tics. These symptoms lasted several seconds. However, the patient exhibited no heart palpitations, chest tightness, dizziness, or other symptoms. His
The patient experienced fever twice at the age of seizures/frontal absences combined with atonic seizures. Respectively, but epileptic seizures still occurred six times carbamazepine (0.6 g per day) were respectively maintained at 80°C. There was no family history of epilepsy or febrile seizure. Development was normal prior to disease onset. He was the first and full-term child born by spontaneous delivery. Physical and intellectual systems were apparently normal. Laboratory data: liver and renal function tests, as well as blood, urine, and stool routine tests, were normal. Chest X-ray, head CT, MRI, and electrocardiogram displayed no abnormalities. Intercital single-photon emission computed tomography failed to identify abnormalities. Intracranial pressure measured by lumbar puncture was 160 mm H2O, and routine tests and biochemical tests of cerebrospinal fluid were normal.

**Video-electroencephalogram monitoring**

BIO-LOGIC128 digital video-electroencephalogram apparatus (USA) was used for recording with a sampling rate of 1 024 Hz and a 10-20 system (Bio-Logic Systems, Mundelein, IL, USA) by two electroencephalogram technicians and a neurologist. Recordings via pre-surgical scalp electrodes lasted 160 hours, and recordings of intracranial electrodes lasted 150 hours. Valproic acid treatment was terminated one week prior to recording, and carbamazepine treatment was terminated during recording.

**Clinical manifestations during video-electroencephalogram monitoring**

Scalp electrodes recorded five epileptic seizures (one during sleep and four while awake) (Table 1). The five seizures were consistent with secondary tonic-clonic seizures described by the family members, but absence-like seizure failed to be recorded.

Table 1: Relationship between sudden cardiac arrest prior to epileptic seizures and EEG/ECG

| Epileptic seizures (time) | Duration of paradoxical discharge before epileptic seizures | EEG display | Duration of paradoxical discharge before cardiac arrest | Duration of cardiac arrest and ECG at the recovery of cardiac beat | Patient’s state at the recovery of cardiac beat |
|--------------------------|------------------------------------------------------------|-------------|----------------------------------------------------------|-------------------------------------------------------------|-----------------------------------------------|
| 1                        | 10 s                                                       | Burst in sleep stage II with generalized high voltage slow wave of 5-6 Hz, dominance in the left frontal pole, and frontal and central areas (Figure 1). | 3 s | Cardiac arrest lasted 12 s, prolongation of R-R interval (2 s, once), 3 s later, normal cardiac rhythm occurred. | Left-leaning head and neck, clonus-like tics of the right upper limb. |
| 2                        | 19 s                                                       | Burst in eyes-closed waking rest with generalized middle-high voltage δ waves of 6-7 Hz, middle-high voltage of 3.5-7 Hz in the right occiput. | 2.5 s | Cardiac arrest lasted 22 s, Arrhythmia lasted 2 s followed by recovery. | Left-leaning head and eyes, tics of both upper limbs. |
| 3                        | 2 s                                                        | Burst in eyes-closed waking rest with generalized α-like fast activities and extremely high voltage slow wave of 4-6 Hz, dominance in the left frontal pole and frontal area. | 2 s | Cardiac arrest lasted 11 s, prolongation of R-R interval (2 s, once), 3 s later, normal cardiac rhythm occurred. | Left-leaning head and eyes, clonus of both upper limbs with forward protrusion. |
| 4                        | 9 s                                                        | Burst in drowsiness with generalized high voltage slow wave of 5-7 Hz, dominance in the left frontal area. Activity artifact interfered with EEG. | 2.5 s | Cardiac arrest lasted 9 s, Arrhythmia lasted 4 s followed by recovery. | Same as the third seizure. |
| 5                        | From a sitting position to a supine position, his body was in movement. | | 3 s | Cardiac arrest lasted 21 s, Arrhythmia lasted 3 s followed by recovery. | Same as the third seizure. |

EEG: Electroencephalogram; ECG: electrocardiogram; s: seconds.
Preoperative monitoring indicated five epileptic seizures. Sudden cardiac arrest occurred 2–19 seconds (mean 8 seconds) prior to epileptic seizures and 2–3 seconds after paradoxical brain discharge bursts and lasted for 12–22 seconds (mean 16 seconds). When cardiac activity was restored, initial clinical symptoms of epileptic seizures occurred. Electroencephalogram results were inaccurate due to activity artifacts from the patient. Electrocardiogram results at recovery revealed arrhythmia (prolongation of R-R interval; Table 1, Figures 1–4).

After the initial sudden cardiac arrest, the patient underwent 24-hour dynamic electrocardiogram, treadmill exercise test, coronary angiography, cardiac CT, and myocardium zymogram examination to exclude cardiac disease, and then continued to receive video-electroencephalogram monitoring.

**Pre-operative evaluation**
Physicians from the Departments of Neurology, Neurosurgery, and electroencephalogram believed that the patient conformed to diagnostic criteria of refractory epilepsy, and sudden cardiac arrest was likely to result in sudden death. Therefore, surgical management was prescribed as soon as possible. Symptoms were produced in the frontal lobe, and brain electroencephalogram showed that discharge likely originated from the median line of the left frontal lobe. To identify the epileptogenic focus, intracranial electrodes were placed in the bilateral longitudinal fissure, the left frontal area, parietal region, the left anterior temporal lobe, and the hippocampus.

**Placement of intracranial electrodes and post-operative video-electroencephalogram monitoring**
A C-shaped incision was made to expose the left frontal and temporal lobes. During surgery, adhesions of cerebral dura mater with arachnoid and cerebral pia mater were visible, as well as arachnoid pachymenia, gray appearance of the brain, and a white mucus-like sediment between the cortical sulci and subarachnoid space (Figure 5A). Cerebral pulsation weakened and the cerebrum felt hard upon palpation. However, at 20 minutes after removal of mucus-like sediment and arachnoid adhesiolysis, the brain surface became red and brain pulsation was significantly enhanced (Figure 5B). Intracranial electrodes revealed that secondary tonic-clonic seizures occurred three times during 150-hour monitoring. It is notable that during the three-time tonic-clonic seizures, the burst of paradoxical discharge originating from the superior parietal lobe and longitudinal crack of frontal lobe were recorded prior to epileptic seizures. In addition, subsequent clinical symptoms were similar to previous symptoms, although cardiac arrest did not occur (Figure 6).
Findings after removal of epileptogenic foci
According to the cortical electroencephalogram, the epileptogenic foci in the left parietal lobe, the left superior frontal gyrus, middle 1/3 region of midfrontal gyrus, and middle region of cingulated gyrus were removed, and a cross-section under the soft membrane was performed in the functional areas. Post-operative recovery was smooth, and the incision healed well. During the 3-month follow-up, no epileptic seizures occurred and only carbamazepine (0.6 g per day) was administered for treatment.

DISCUSSION

In 1954, Phizackerley et al[3] was the first to observe that epileptic seizures could lead to cardiac arrest. In 1992, Liedholm et al[4] reported that cardiac arrest occurred when precursory symptoms and paradoxical brain discharge occurred. Specifically, cardiac arrest lasted for 17 seconds in a patient with complex partial seizure; following implantation of a cardiac pacemaker, cardiac arrest did not reappear. In 2007, Leung et al[5] stimulated the left cingulated gyrus with an intracranial electrode to induce sudden cardiac arrest in a patient with frontal lobe epilepsy. Discharges generated by the frontal lobe or temporal lobe can induce sudden cardiac arrest, although the exact mechanisms remain unclear. Fatal arrhythmia and central respiratory depression are considered to be important causes of death in patients with epilepsy[6-8]. In 1999, Goodman et al[9] observed that heart rate decreased and blood pressure increased during epileptic seizure in a rat model of amygdala kindling; this phenomenon was believed to be due to electric kindling activation of sympathetic and parasympathetic nerves. Previous results have shown that parasympathetic activity decreases and sympathetic activity increases within 30 seconds prior to epileptic seizure in patients with temporal epilepsy, which suggests that epileptic seizures induce dysfunction of the cardiac autonomic nerve regulation center, thereby inducing sudden death[10].

In the present study, the patient did not die, but the possibility for sudden death was great. Each paradoxical brain discharge that occurred prior to epileptic seizures led to cardiac arrest, one of which lasted for 22 seconds (longest duration of cardiac arrest). Self-recovery of a normal rate was associated with age and the lack of other underlying heart diseases. Cardiac arrest occurred prior to clinical epilepsy symptoms, not during the tonic-clonic seizures, which suggested that cardiac arrest was not due to cerebral hypoxia or a dysfunctional regulation center of the cardiac autonomic nerve. Each cardiac arrest correlated with paradoxical brain discharges. Cardiac arrest suddenly occurred within 2-3 seconds after paradoxical brain burst discharges, and at that time, clinical symptoms of epileptic seizures were not present. In addition, following the five documented cardiac arrests, the heart rate was completely restored when clinical symptoms of epileptic seizures were obvious. These results suggested that paradoxical brain discharge activated brain mechanisms to induce cardiac arrest, instead of symptoms of epileptic seizures.

Pathology indicated hyaline degeneration of collagen fibers of cerebral dura mater, focal arachnoid pachymenia, small blood vessel hyperplasia, and inflammatory cell infiltration, but brain cells were normal. The pathological diagnosis indicated chronic inflammation.
electrodes were in place, mucus-like substances and poor circulation on the cerebral surface were visible. Post-operative pathology confirmed meningeal chronic inflammatory hyperplasia. Following removal of the mucus-like substances and elimination of focal brain high pressure, circulation to the cerebral surface was restored. At the epileptogenic foci, although bursts of paradoxical discharge and epileptic seizures were present, cardiac arrest did not occur. It was hypothesized that the mucus-like substances were strongly associated with sudden cardiac arrest and epilepsy was due to meningitis (the patient had single history of febrile convulsions). Stimulation of mucus-like substances results in poor circulation on the cerebral surface, leading to abnormal cellular functions and subsequent paradoxical discharge and epileptic seizures. In addition, mucus-like substances on the cerebral surface induced focal poor circulation of subarachnoid cerebrospinal fluid, resulting in local high pressure and poor blood supply to the brain. Because the lesions within the subarachnoid space were relatively limited in space, focal high pressure did not necessarily lead to intracranial hypertension. Intracranial pressure, as measured by lumbar puncture, was 1.569 kPa. In addition, focal high pressure on the cerebral surface was present. During surgery, poor blood circulation on the cerebral surface and weakened cerebral pulsation was visible. However, following decompression, these phenomena disappeared. It is possible that cardiac arrest correlated with focal high pressure and poor blood circulation. Each cardiac arrest was associated with paradoxical brain discharge. It is possible that sudden paradoxical brain discharge induced a brain regulation center (the position of the regulation center remains currently unknown) to relieve focal brain pressure by initiating cardiac arrest. This mechanism was sometimes effective (such as absence-like seizures). However, when the discharge was enhanced and spread throughout the brain, secondary tonic-clonic seizures occurred. Self-recovery of heart rate was associated with reflex mechanisms within the cardiovascular center under hypoxic conditions. Although this hypothesis fails to completely explain cardiac arrest in the present patient, evidence suggested that refractory secondary epilepsy correlated with sudden cardiac arrest. Cortical electroencephalogram and deep intracranial electroencephalogram is necessary to locate the focus and pathogen, as well as provide surgical treatment. Sudden cardiac arrest could occur in epilepsy patients, although the mechanisms remain unclear. In individual patients with epilepsy, paradoxical brain discharges could result in cardiac arrest prior to epileptic seizures. However, elimination of focal brain high pressure could prevent cardiac arrest.

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