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CASE REPORT

PATHOLOGY/BIOLOGY

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Early Repolarization, Acute Emotional Stress and Sudden Death

ABSTRACT: We herein report the case of a 36-year-old man who died suddenly after a fight with another man. Forensic investigations included unenhanced computed tomography, postmortem angiography, autopsy, histology, neuropathology, toxicology, and biochemistry and allowed a traumatic cause of death to be excluded. An electrocardiogram recorded some years prior to death revealed the presence of an early repolarization pattern. Based on the results of all investigations, the cause of death was determined to be cardiac arrhythmia and cardiac arrest during an emotionally stressful event associated with physical assault. Direct third party involvement, however, was excluded, and the manner of death was listed as natural. The case was not pursued any further by the public prosecutor.

KEYWORDS: forensic science, early repolarization, idiopathic ventricular fibrillation, sudden death, emotional stress, postmortem biochemistry

Early repolarization (ER) is a common electrocardiographic pattern characterized by an elevation of the QRS-ST junction (J wave) in at least two leads. The amplitude of J-point elevation must be at least 1 mm (0.1 mV) above baseline levels, either as QRS slurring or notching in the inferior or lateral leads. Though considered a benign electrocardiogram (ECG) manifestation for years, the presence of this pattern has recently been recognized in some studies as associated with unexplained syncope or sudden cardiac death due to ventricular fibrillation vulnerability (1–4).

In a study performed in 2008, Haïssaguerre et al. (2) reviewed clinical data from 206 patients who were resuscitated after cardiac arrest due to idiopathic ventricular fibrillation and 412 subjects without heart disease, to assess the prevalence of electrocardiographic ER. Their results showed that ER was significantly more frequent in patients with idiopathic ventricular fibrillation than in control subjects, suggesting a relationship between ER and sudden cardiac arrest. Furthermore, among case subjects, those with ER were more likely to be male and have a history of syncope or cardiac arrest during sleep. The authors postulated that this repolarization abnormality could be a marker of an underlying electrical vulnerability increasing the risk of fatal arrhythmias under particular conditions, thereby responsible for a proportion of unexplained sudden deaths. This would pertain predominantly to cases of young men, as reported by several authors.

Acute and chronic emotional stress is known to cause neurovegetative alterations inducing transitory or persisting bodily dysfunctions. The neurovegetative changes deriving from such stresses may include the hemodynamic response, autonomic alterations, neuroendocrine activation as well as inflammatory and prothrombotic responses, which have a potentially negative influence on the cardiovascular system (5). The increased frequency of sudden death after emotionally devastating disasters, such as earthquakes, wars, and terrorist attacks, has long suggested that emotional distresses may play a role in acute coronary syndromes and arrhythmias, primarily in those with predisposing, cardiac conditions (6,7). Furthermore, numerous authors have reported cases in which the sudden deaths of individuals with underlying cardiac disease were postulated as having been caused by arrhythmic episodes precipitated by physical and/or emotional stresses (7–12).

In this article, we describe the case of a 36-year-old man of North African origin who suddenly lost consciousness and died while seated in an ambulance, talking to the first-aid workers. He had been fighting immediately prior with another man in the street. Numerous witnesses were present. Forensic investigations ordered by the public prosecutor included unenhanced CT-scan, postmortem angiography, autopsy, histology, neuropathology, toxicology, and biochemistry. These results allowed a traumatic cause of death to be excluded. ECGs recorded some years prior were obtained by the local health services and revealed an early repolarization pattern. Despite medicolegal investigations, the cause of death was not precisely determined although the hypothesis of an arrhythmia precipitated by physical and emotional stress in a person presenting an underlying, predisposing electrocardiographic pattern (ER) was thereby privileged.

Case Report

According to witness records, two young men were violently arguing in the street in the afternoon and suddenly started

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fighting. They physically fought, exchanged blows, and sprayed each other in the face with pepper sprays. One of them started running and was kicked directly in the back by the other, falling to the ground. He was then punched twice in the face but did not lose consciousness. He stayed on the ground, while the other man ran away upon hearing the police sirens. The witnesses called an ambulance and a police car, which arrived at the scene a few minutes later. First-aid workers helped the man to stand up. They described him as being extremely excited but conscious and cooperative. In a very confused way he claimed that he had been punched twice in the face and was sprayed in the eyes with a spray. First-aid workers and policemen did not notice any suspicious odor suggesting a teargas grenade. Conjunctiva and sclera of the man were examined on place by the physician and looked normal, whereas respiratory rate appeared increased. He did not complain of any chest pain. The man was immediately transferred in the ambulance for clinical examination and ECG recording. While sitting on a patient cart, talking to the first-aid workers, and taking off his jacket, he suddenly lost consciousness, dying minutes thereafter despite resuscitation attempts. Due to unclear circumstances of death and the potential involvement of a third party, a medicolegal autopsy was ordered by the public prosecutor.

Radiology, External Examination and Autopsy

Unenhanced computed tomography and postmortem computed tomography angiography were performed prior to autopsy and revealed losses of contrast agent in the left quadratus lumborum and both biceps muscles, likely corresponding to hemorrhages of traumatic origin. No pneumothorax was depicted. External examination revealed the presence of bruises and excoriations of the skin on different body parts (face, internal side of the lips, neck, upper and lower limbs) as well as fresh injection mark (medical intervention) at the left upper limb and cardiopulmonary resuscitation marks on the chest. No bleeding wounds were observed at any site. Rigor mortis was present in the major and minor joints. Reddish purple postmortem lividity was present on the body posteriorly and could not be eliminated by finger pressure. The man was 183 cm tall and weighed 80 kg. Internal examination revealed the presence of hemorrhages of the left temporal and both biceps muscles. The left and right pectoralis major and pectoralis minor muscles as well as the left first intercostal space showed hemorrhagic infiltrations. These findings were consistent with cardiopulmonary resuscitation marks. The heart weighted 440 g and did not reveal any hypertrophy or dilatation. The coronary arteries and aorta were unremarkable, with no sign of aortic dissection. The lungs were relatively congested (right lung 770 g, left lung 690 g) and did not show any injury. Pulmonary embolism was not observed. Hemothorax, hemomediastinum, hemopericardium, or hemoperitoneum were not observed. No identifiable pill components or fragments were found in the stomach contents or upper gastrointestinal tract. The brain did not reveal any abnormalities. The spleen, liver, and kidneys did not show any significant, macroscopic changes. No other abnormalities were detected elsewhere in the body.

Histology, Neuropathology, Toxicology, and Biochemistry

Microscopically, the heart revealed no evidence of contraction band necrosis, subendocardial hemorrhage, or acute myocardial ischemia. Histology showed areas of fatty degeneration of the liver, hyalinized glomeruli in the kidneys and generalized organ congestion. The lungs showed alveolar and interstitial macrophages containing anthracotic pigment, peripheral emphysema, and desquamation of the ciliated respiratory epithelium. Neuropathology was unremarkable.

Peripheral blood from the femoral vein, cardiac blood, bile, vitreous humor, urine, cerebrospinal, and pericardial fluids as well as gastric content, hair, and samples of certain tissues (liver, kidney, and skeletal muscle) were recovered for toxicological and biochemical analyses. Swabs were also taken from the skin of the face. Toxicological tests were performed in blood, urine, and swabs taken at autopsy. The pump bottle spray found on the death scene was transferred to the medicolegal center for toxicological investigations.

Toxicology included ethanol determination and general unknown screening for common drugs (in particular sympathomimetic drugs such as ephedrine, cathinone, cocaine, amphetamines, and "designer drugs") and illegal substances by gas chromatography mass spectrometry (GC-MS) using commercial mass spectrum libraries, high-performance liquid chromatography with diode array detection (HPLC-DAD), and headspace gas chromatography flame ionization detection (HS-GC-FID). Toxicological analysis revealed the presence of mirtazapine (within therapeutic range), tetrahydrocannabinol, and its metabolites in blood and mirtazapine and its metabolites in urine. Ethanol was not detectable in blood. Skin swabs were negative. The content of the pump bottle spray underwent toxicological tests. The results revealed the presence of capsaicin, dihydrocapsaicin and related capsaicinoids.

Biochemical investigations were performed in femoral blood, postmortem serum from femoral blood, and vitreous humor and included measurements of tryptase, procalcitonin, C-reactive protein, lipopolysaccharide-binding protein, sCD14 subtype, glucose, sodium, chloride, 3-β-hydroxybutyrate, markers of renal (urea nitrogen, uric acid, and creatinine), hepatic (total proteins, albumin), and cardiac (troponin I, N-terminal pro-brain natriuretic peptide) functions. The analyses did not show any significant results.

Other Investigations

The victim's medical history was unremarkable, and there was no evidence of cardiovascular or other serious diseases. The patient had never noticed any cardiac symptoms, in particular no anginal discomfort, arrhythmia, or episodes of cardiac syncope, and no regular medication was taken. Family history was also negative for cardiovascular diseases. Social history was significant for tobacco smoking (a pack of cigarettes a day) started at age 16, use of occasional alcohol, recreational marijuana abuse, and intermittent incarcerations.

An ECG recorded during a routine follow-up 2 years prior to death was obtained from the local health services and mentioned the presence of J waves in the inferolateral leads. This ECG was also examined by our consultant cardiologist who confirmed the presence of an ER pattern (Fig. 1).

Based on the results of all investigations, the cause of death was determined to be cardiac arrhythmia and cardiac arrest during an emotionally stressful event and associated with a physical assault. Direct third party involvement was, however, excluded, and the manner of death was listed as natural. The case was not pursued any further by the public prosecutor.

Discussion

Throughout recorded history, emotional and stress-related psychosocial factors have been associated with sudden death.

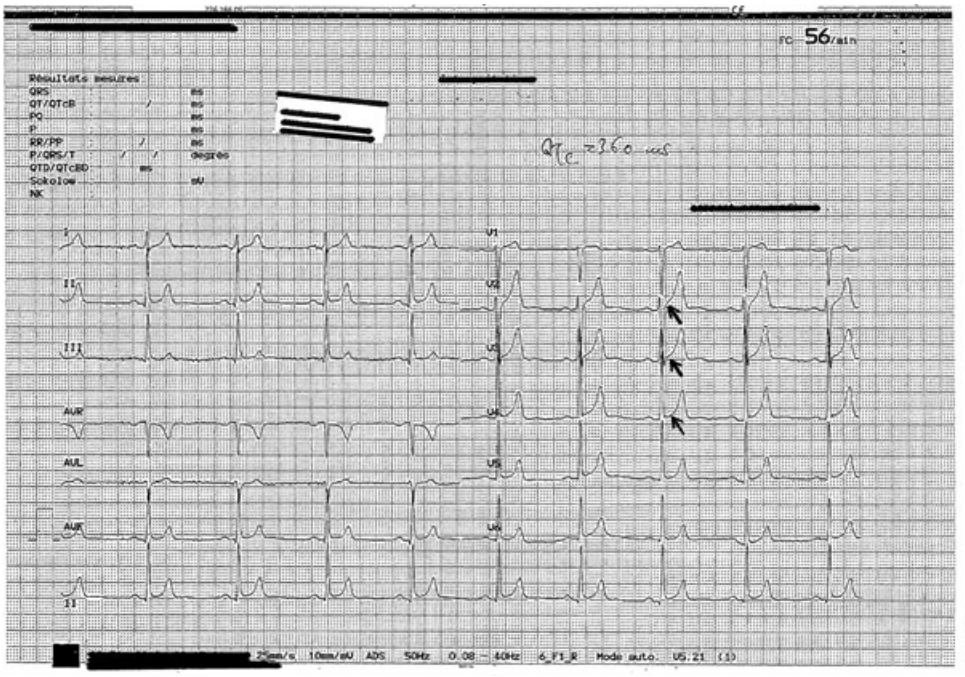

FIG. 1—*The electrocardiogram obtained from the local health services and recorded 2 years prior to death. The arrows indicate the elevation of the QRS-ST junction (J wave).*

Ancient scripts and scrolls have contained references to this relationship long before any scientific understanding had been reached pertaining to the influence of these factors on cardiac pathophysiology. Diogenes Laertius recounts the episode according to which Chilon of Lacedaemon died from joy when he embraced his son who had just attained an Olympic boxing triumph (13).

In the recent past, several studies have shown increased sudden deaths from cardiac complications after acute psychological stress, intense emotional upset of unforeseen devastating disasters such as earthquakes, terrorist attacks, and war. Along similar lines, a pattern of increased hospital admission for acute myocardial infarction was reported in England on the day of the country's 1998 World Cup soccer match against Argentina. This match involved a penalty shoot-out, and England lost (5,6,13–22).

In the realm of forensic pathology, Cebelin and Hirsch (23) reviewed homicidal assaults that occurred in Cleveland (Cuyahoga County, OH) over 30 years focusing on autopsy and investigative findings relating to victims who died as a direct result of physical assaults without sustaining internal injuries. According to the authors, these data supported the hypothesis that catecholamine mediation had a role in determining myocardial changes, which were comparable to those described in the myocardium of stressed animal used in the experiments. Based on these results, the authors concluded that stressful events were a factor potentially leading to death through their effects on the cardiovascular system. Thereafter, medicolegal literature has mentioned numerous cases of so-called homicide by heart attack, in which the sudden deaths of people with underlying cardiac disease were thought to be caused by arrhythmias precipitated by physical and/or emotional stress induced by the criminal activity of another person (7–12).

The pathways through which psychological stress and emotional upset may lead to sudden death has been experimentally studied and tested. Psychological stress has been compared with physical exertion, sexual activity, sleep disturbance, tobacco smoking, alcoholic, and caffeinated beverage consumption. The activation of the sympathetic nervous system induced by stressful events has been indicated as the underlying cause of cardiovascular complications potentially leading to sudden death (5,8,14,24,25).

Indeed, acute sympathetic nervous system activation increases blood catecholamine levels, cardiac output, and blood flow in direct response to increased metabolic workload. This appropriate physiologic response is not typically associated with adverse outcomes unless there is preexisting coronary disease, severe hypertrophic cardiomyopathy, chronic heart failure, or underlying disturbances of the cardiac rhythm (14,19).

Significant adverse effects of acute emotional stress on the heart can be broadly divided into three areas: left ventricular contractile dysfunctions, myocardial ischemia, and cardiac rhythm disturbances. Although these abnormalities are often only transient, their consequences can be gravely damaging and sometimes fatal. High levels of catecholamines resulting from acutely stressful episodes are thought to be at the origin of left ventricular dysfunctions (for instance, takotsubo cardiomyopathy) (26,27).

Emotional stress-induced myocardial ischemia is likely the consequence of sympathetic hyperactivation produced by acute emotional stress through regional myocardium motion abnormalities, even in individuals with no evidence of underlying cardiovascular disease. Lastly, recent studies have indicated that asymmetric brain activity could be particularly important in making the heart more vulnerable to developing ventricular arrhythmias. Indeed, lateralization of cortical and subcortical cerebral activity during emotional stress may stimulate the heart asymmetrically, producing areas of inhomogeneous repolarization that create electrical instability and thus facilitate the onset of cardiac arrhythmias (8,28).

Many neurological, psychiatric, and cardiologic patient groups are at risk of arrhythmias and sudden death attributable to central neurogenic causes. For example, sudden arrhythmic death in epilepsy is likely to originate from seizure activity driving different autonomic effects on the heart. Analogously, emotional challenges as well as mental and physical stresses could be associated with arrhythmogenesis, again via efferent autonomic activity, especially in patients with preexisting cardiac disease (28–32).

Electrophysiological studies suggested that increased electrical inhomogeneity of the myocardium during the repolarization phase of the cardiac cycle is a major factor in the ventricular arrhythmia susceptibility. The left- and right-sided autonomic nerves are distributed asymmetrically over the heart ventricles and unilateral stimulation of either side may alter repolarization inhomogeneity. Thus, repolarization inhomogeneity may reflect "upstream" influences on the right–left symmetry of sympathetic cardiac drive, for example asymmetric brain activation in response to stress (28,33,34).

Numerous studies have investigated the influence of frustrating and anxiety-producing events, positive emotions as well as usual daily activities on the QT interval (35–37). Lane et al. (37) observed that typical daily emotions had a definable effect on cardiac repolarization in subjects with a long QT interval, leading to the conclusion that emotion-related repolarization changes were among the multiple factors that potentially contributed to arrhythmic cardiac events in patients with long QT intervals.

The J-point deflection, also known as the Osborn wave or J wave, occurs at the QRS-ST junction and was first described by Tomaszewski in 1938. An ER pattern with slurring or notching at the terminal part of the QRS complex on the ECG was first described in 1936. It used to be a wide-held belief that ER on ECG was not associated with any adversity. During the past decade, however, a number of clinical reports have described patients with idiopathic ventricular fibrillation and sudden cardiac arrest associated with abnormal J waves. In these patients, ER was reported as the only "abnormal" ECG finding (3).

More definitive clinical evidence and a turning point in the perception of ER came in 2008 when Haïssaguerre et al. (2) reported a high prevalence of ER in patients with idiopathic ventricular fibrillation. Bonny et al. (4) reported in 2009, the case of a 39-year-old black African male, nonelite athlete, who lost consciousness while playing football. A systematic checkup with the ECG performed 1 year before this episode displayed an ER pattern confirmed by the ECG recorded in the hospital during the cardiac evaluation postsyncope.

Burashnikov et al. (38) published in 2010, the results of a study population performed on 205 subjects diagnosed with Brugada syndrome, idiopathic ventricular fibrillation, and early repolarization syndrome to identify mutations in the subunits of the L-type calcium channel (LTCC). The authors found mutations in all the three subunits of the LTCCs in a relatively high percentage of subjects.

In the case herein presented, extensive investigations including unenhanced computed tomography, postmortem angiography, autopsy, histology, neuropathology, toxicology, and biochemistry were performed. Radiology and macroscopy results allowed traumatic causes of death to be excluded. Neuropathology and histology findings failed to be conclusive. Toxicological and biochemical analyses did not reveal any significant results. Based on medical records (ECG showing ER pattern) and circumstantial data (sudden loss of consciousness and cardiac arrest), we formulated the hypothesis that physical exertion and acute emotional stress related to fighting had played a role as arrhythmogenic factors, leading to or contributing to death.

In the study of Haïssaguerre et al. (2), case subjects with ER were more likely to be male and have a history of unexplained syncope or sudden cardiac arrest during sleep, while few cases belonged to the subgroups for which a high prevalence of ER was reported in the literature (e.g. athletes and blacks). In the case reported by Bonny et al. (4), the loss of consciousness occurred while the man was playing football.

In our case study, the repolarization abnormality in itself could have been responsible for the sudden unexplained death of the patient, without any contributing role of physical and psychological stress. However, as stressful events are thought to increase the risk of fatal arrhythmias and ER may be considered a marker of an underlying electrical vulnerability, both factors may have contributed in determining or precipitating the arrhythmic episode finally responsible for the death.

Lastly, this case highlights the importance of considering all potentially relevant data to formulate appropriate hypotheses concerning the cause of death. Indeed, only the correlation of scene investigation elements, radiology observations, autopsy findings, toxicological, and biochemical results as well as medical and social histories of the deceased when available can allow the conclusion of a natural death to be reached despite the absence of identifiable anatomic, toxicological, and metabolic causes of death.

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