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Abstract:
Excited (or agitated) delirium is characterized by agitation, aggression, acute distress and sudden death, often in the pre-hospital care setting. It is typically associated with the use of drugs that alter dopamine processing, hyperthermia, and, most notably, sometimes with death of the affected person in the custody of law enforcement. Subjects typically die from cardiopulmonary arrest, although the cause is debated. Unfortunately an adequate treatment plan has yet to be established, in part due to the fact that most patients die before hospital arrival. While there is still much to be discovered about the pathophysiology and treatment, it is hoped that this extensive review will provide both police and medical personnel with the information necessary to recognize and respond appropriately to excited delirium. [West J Emerg Med. 2011;12(1):77-83.]

Excited Delirium

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Excited (or agitated) delirium is characterized by agitation, aggression, acute distress and sudden death, often in the pre-hospital care setting. It is typically associated with the use of drugs that alter dopamine processing, hyperthermia, and, most notably, sometimes with death of the affected person in the custody of law enforcement. Subjects typically die from cardiopulmonary arrest, although the cause is debated. Unfortunately an adequate treatment plan has yet to be established, in part due to the fact that most patients die before hospital arrival. While there is still much to be discovered about the pathophysiology and treatment, it is hoped that this extensive review will provide both police and medical personnel with the information necessary to recognize and respond appropriately to excited delirium. [West J Emerg Med. 2011;12(1):77-83.]

INTRODUCTION

Excited delirium (EXD), first described in the mid 1800's, has been referred to by many other names – Bell's mania, lethal catatonia, acute exhaustive mania and agitated delirium.[1] Regardless of the label used, all accounts describe almost the exact same sequence of events: delirium with agitation (fear, panic, shouting, violence and hyperactivity), sudden cessation of struggle, respiratory arrest and death.[2] In the majority of cases unexpected strength and signs of hyperthermia are described as well.[3,4].While the incidence of EXD is not known, the purpose of this review is to identify what is known or suspected about the pathophysiology, outcomes and management options associated with EXD to assist medical professionals in the future.

Issues Regarding EXD

EXD has gained increasing public attention recently due to the number of post-mortem explanations offered by medical examiners regarding the death of individuals being restrained by police or being taken into custody. This diagnosis has caused concern because EXD is not a currently recognized medical or psychiatric diagnosis according to either the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-IVTR) of the American Psychiatric Association or the International Classification of Diseases (ICD-9) of the World Health Organization. Likewise, the authors of one review article found enough evidence in the literature to suggest that excited delirium, rhabdomyolysis and neuroleptic malignant syndrome might represent the clinical spectrum of a single disease.[5] Although more research is needed to elucidate cause and effect, it is important to note that a lack of recognition of the condition in the context of law enforcement activities does not negate the significance of the behavioral and physical signs referred to as EXD. For instance, one important study found that only 18 of 214 individuals identified as having EXD died while being restrained or taken into custody.[6] If anything, the possible association with other life-threatening syndromes only gives impetus to the need for critical emergency medical intervention when encountering a person thought to be in a state of excited delirium.

Background

Although reports of patients with similar symptoms first appeared in the 19th century, the first modern mention of EXD was in 1985.[3] The presentation of excited delirium occurs with a sudden onset, with symptoms of bizarre and/or aggressive behavior, shouting, paranoia, panic, violence toward others, unexpected physical strength and hyperthermia. An extensive review of reported case series reveals that in a majority of cases EXD was precipitated by stimulant drug use and in much fewer cases psychiatric illness (such as mania, depression, or schizophrenia) or systemic illness.[7-9]

Methamphetamine, PCP and LSD have been reported in a few series, but by far the most prevalent drug of abuse found on toxicology screening was cocaine.[10] Since the victims frequently die while being restrained or in the custody of law enforcement, there has been speculation over the years of police brutality being the underlying cause. However, it is important to note that the vast majority of deaths occur suddenly prior to capture, in the emergency department (ED), or unwitnessed at home.

Prior to 1985 most reported cases of sudden death from cocaine intoxication involved "body stuffers" who died secondary to massively high exposure to the drug after packets they were carrying burst. A report published by Wetli and Fishbain [3] in 1985 was one of the first case series to examine recreational cocaine users who died following episodes of excited delirium. They noticed that these deaths differed in both presentation and average blood cocaine concentrations from typical cocaine overdose fatalities. In fact, cases of agitated delirium were often associated with lower blood levels of cocaine. Explorations by Pollanen et al[9] and Ruttenber et al[11] showed blood levels of cocaine in EXD cases to be similar to levels found in recreational cocaine users and much lower than levels found in people who died from cocaine associated intoxication. Moreover, the reports found that the blood levels of benzoylecgonine, the primary metabolite of cocaine, in the cocaine-associated EXD cases were higher than in recreational users, suggesting the cocaine use prior to death was consistent with recent "binge" use. More recently, Stephens et al.,[12] in an analysis of the significance of cocaine upon a specific death, confirmed that a pattern of chronic cocaine use characterized by repeated binges is associated with the development of fatal EXD.

PATHOPHYSIOLOGY

Cocaine has many neurotransmitter affects on the brain, including the blockade of all monamine neurotransmitters via its interaction with the various transporters. The reinforcing or addictive properties of cocaine are primarily attributed to increased dopamine levels. Dopamine is an essential neurotransmitter in several neural pathways regulating movement, hypothalamic function, positive behavioral reinforcement and higher cognitive function. The mesolimbic pathway, which connects the nucleus accumbens and tegmentum, is most critical for reinforcement and addiction to psycho-stimulants. Several researchers have suggested that cocaine use may cause aberrant dopamine processing in the mesolimbic pathway and elsewhere in the brain, resulting in hyperactivity and hyperthermia.[11,13] Additionally, in cases of EXD, dopamine processing has been shown to be further altered compared to non-psychotic cocaine users. Recent research has identified several possible explanations for this critical difference.

First, Mash et al[14] discovered evidence of increased alpha α-synuclein, a native protein and major component of Lewy bodies in Parkinson's disease, in midbrain dopamine neurons of chronic non-psychotic cocaine users.[2] *In vivo*, increased binding of α-synuclein to dopamine transporters has been shown to increase dopamine uptake and dopamine mediated apoptosis, leading to irreversible neuroadaptive changes. The authors suggested that the increased α-synuclein deposition might occur as a protective response due to high dopamine recycling and oxidative stress from cocaine abuse. Their postmortem research demonstrated that chronic non-psychotic cocaine users, compared to control non-drug users, had markedly elevated presynaptic α-synuclein levels in the substantia nigra and ventral tegmental area of the midbrain. However, compared to the same control group, victims of fatal EXD showed decreased levels of α-synuclein in the substantia nigra and only slightly increased levels in the ventral tegmental area. This discovery suggests that EXD victims might have a different pattern of α-synuclein regulation and perhaps lack normal compensatory measures for dealing with rapidly elevating dopamine levels.

Second, multiple studies have documented dopamine transporter binding sites that are increased in human chronic cocaine users.[15-17] Mash et al[18] used *in vitro* autoradiography and ligand binding studies to map and measure D3 dopamine and kappa 2 opioid receptors in brain tissue from postmortem cocaine overdose victims and compared them to fatal EXD victims. The D3 receptor subtype has a distinctive neuroanatomy pattern in the normal human brain, with high densities in areas associated with the pattern-building, euphoric effects of cocaine, such as, the nucleus accumbens and limbic sectors of caudate and putamen. The authors found that chronic cocaine abuse lead to an adaptive elevation of D3 dopamine receptors (2-3 times vs. control) and kappa 2 opioid receptors (2 times vs. control) in the nucleus accumbens and associated limbic regions. By contrast, cocaine abusing EXD victims did not demonstrate increased density for D3 receptor binding. This finding mirrored similar results by Staley et al[19] that failed to demonstrate an elevation in dopamine transporters in the striatum of EXD victims versus aged-matched drug-free control patients. Mash et al[18] suggested that the lack of compensatory changes in the EXD victims could be related to concurrent psychiatric co -morbidity, recent "binge" cocaine use, or aberrant molecular processing of D3 receptor mRNA. Interestingly, different mRNA species have been found in the cerebral cortices of chronic schizophrenia patients, which raise the possibility that similar alterations in D3 receptor processing could be involved in EXD victims.[20]

Third, further investigation by Mash et al[22] focused on the functional activity of dopamine transporters, which were previously found to be elevated in the limbic system of chronic cocaine abusers.[18,21] Using cryopreserved tissue samples from aged-matched chronic cocaine users (n=10), EXD victims (n=8) and control subjects (n=10), the authors quantified the number of dopamine transporters in parallel to dopamine uptake and discovered dopamine uptake was

twofold in the ventral striatum from chronic cocaine users versus aged-matched controls. Victims of fatal EXD failed to demonstrate an increase in dopamine transport function, despite having a history of cocaine use and post-mortem blood elevations of cocaine and benzoylecgonine. Based on the results, chronic cocaine use seems to cause a compensatory increase in dopamine transporters, which would decrease the amount of dopamine available to potentially over stimulate the post-synaptic receptors. This effect, which may be neuron protective, is lacking in fatal EXD victims.

In addition to altering dopamine reuptake directly, cocaine has been shown to potently inhibit serotonin reuptake, thus elevating synaptic levels of the neurotransmitter.[22] Despite the relative certainty that dopamine is the primary substrate mediating the reinforcing and addictive properties of cocaine, a study by Rocha et al[23] of dopamine transporter knockout mice suggests the involvement of serotonergic brain regions in the initiation and maintenance of cocaine self-administration and withdrawal symptoms. Meanwhile, serotonin has been implicated as an independent modulator of dopaminergic neurotransmission. Mash et al[24] compared serotonin transporter density in brain tissue from cocaine overdose victims and cocaine-associated EXD victims, finding that the transporters localized to the dopamine rich substantia nigra and striatum in response to chronic cocaine use. Once again, EXD victims failed to display an up regulation of serotonin transporters within aforementioned brain regions.

Lastly, in a 2009 case series of an unprecedented ninety fatal EXD victims, Mash et al[25] conducted a post-mortem quantitative analysis of dopamine transporters and heat shock protein 70. Incident circumstances, force measures, autopsy and toxicology results were determined and controlled in the analysis. Mean core body temperature among the ninety victims was 40.7°Celsius and, although the majority tested positive for cocaine, four had no licit or illicit drugs or alcohol found at autopsy. The authors discovered heat shock proteins were elevated 1.8-4 fold in postmortem brain tissue, confirming that hyperthermia is an associated symptom and indication of fatal autonomic dysfunction in the victims. In addition, dopamine transporter levels were decreased compared to age-matched controls, which correlate with the findings by previous authors of aberrant dopamine signaling in EXD.

These observations demonstrate that cocaine affects a number of different neurochemical substrates in the brain and suggest that chronic exposure may lead to complex neuroadaptations within discrete brain loci. Furthermore, compared to non-psychotic cocaine overdose victims, fatal EXD victims have been shown to possess alterations in neuroanatomy and neurophysiology that may represent a subtype of patient with an altogether unusual genotype and/or phenotype; one characterized by high dopamine levels and a hyperactive autonomic nervous system. This understanding may lead to changes in the recognition, handling and acute treatment of EXD by first responders and emergency physicians.

OUTCOMES

Approximately two thirds of EXD victims die at the scene or during transport by paramedics or police.[26] Victims who do not immediately come to police attention are often found dead in the bathroom surrounded by wet towels and/or clothing and empty ice trays, apparently succumbing during failed attempts to rapidly cool down.[2] It appears that in all cases, victims died of either respiratory arrest or fatal cardiac dysrrhythmia. Diagnoses were supported by postmortem exams showing pulmonary and cerebral edema with nonlethal self-inflicted injuries.[3,10,27,28] The few who live long enough to be hospitalized often succumb to disseminated intravascular coagulation, rhabdomyolysis and renal failure.[2] These fatal cardiopulmonary changes are thought to be the result of increased catecholamine stress on the heart, myocardial hypertrophy, microangiopathy and fatal arrhythmias.[3,10] The proposed cause of these changes is debated.

Since the victims sometimes die in police custody, the most widely publicized proposed causes of death in EXD are taser use and positional asphyxia. No study thus far has been able to demonstrate a causal relationship between Taser use and subsequent individuals' deaths.[10,28] In one study of 32 healthy police volunteers, a 12-lead electrocardiogram was performed at baseline and then repeated within 60 seconds post-exposure to a one to five second shock by the Taser X26.[29] The authors reported no instances of dysrhythmia nor ectopy among the subjects. Furthermore, no statistically significant changes were noted in the QRS duration, QT and QTc intervals. These results corroborate with previous reports using single-lead monitoring to assess cardiac changes before, during, and after Taser activation.[30,31]

As mentioned before, people experiencing EXD are highly agitated, violent, and show signs of unexpected strength so it is not surprising that most require physical restraint. The prone maximal restraint position (PMRP, also known as "hobble" or "hogtie"), where the person's ankles and wrists are bound together behind their back, has been used extensively by field personnel. In far fewer cases, persons have been tied to a hospital gurney or manually held prone with knee pressure on the back or neck.[6,9,10,26] Supporters of the positional asphyxia hypothesis postulate that an anoxic death results from the combination of increased oxygen demand with a failure to maintain a patent airway and/or inhibition of chest wall and diaphragmatic movement.[9,10] This explanation has been further supported by coroners' reports of "positional asphyxia" as the cause of death in multiple fatal EXD cases.

The positional asphyxia theory has been refuted by a series of articles by Chan et al[32] exploring the effect of PRMP on ventilatory capacity and arterial blood gases. In one study of fifteen healthy male volunteers, the authors found a small, but statistically significant decline in forced vital capacity

(FVC), forced expiratory volume in one second (FEV1) and maximal minute ventilation (MVV) comparing sitting to restrained positions. However, there was no evidence of hypoxia (mean oxygen tension [PO2] less than 95 mmHg or co-oximetry less than 96%) in either position, nor was there a significant difference in PCO2, heart rate recovery or oxygen saturation. In another study, the authors sought to determine the effect of adding 25 and 50 pounds weight force on respiratory function of healthy volunteers in the PRMP.[33] Validating earlier results, they found FVC/FEV1 was significantly lower in restrained positions versus sitting, but not significantly different between restrained positions with and without weight force. Furthermore, they found mean oxygen saturation levels were above 95% and mean end-tidal CO_2 levels were below 45 mmHg for all positions, regardless of weight force. Based on these findings, PMRP may result in a transient pattern of restricted pulmonary function, but the lack of evidence for hypoxia or hypoventilation suggests that factors other than body positioning appear to be more important determinants for sudden, unexpected death. Nonetheless, respiratory muscle fatigue resulting from exertion and struggle against restraints (exertion vs. position asphyxia) cannot be excluded nor can potentially fatal pre-existing problems with central cardiac output, oxygen saturation, or oxygen use.[6,26,28,34]

Another potential cause of death is cardio toxicity due to chronic cocaine abuse. Preexisting coronary artery disease appears to account for many of the deaths, as does the contribution of cocaine acting as a potent adrenergic agonist, but the mechanism is likely more complex.[27] A larger case series published in 2006 noted that more than half of EXD fatalities were found to have some degree of cardiovascular disease.[28] Since the majority of deaths occur after prolonged drug use, it is thought that cocaine initiates a series of detrimental changes to the heart that might take years to express. These changes may be due to long-term catecholamine toxicity and include cardiac hypertrophy, microangiopathy and myocardial fibrosis.[35] Electrocardiographic and autopsy studies confirm that the heart weight of cocaine users, is, on average, ten percent greater than expected values.[36,37] It is not clear how cocaine initiates the process of hypertrophy, but it could be due to the direct oxidant effect of cocaine or cocaine-induced hypertension. Either way, research using rats injected with cocaine demonstrated increases in levels of mRNA coding for atrial naturetic factor, collagen and alpha/beta myosin.[38]

Small intramyocardial arteries are often thickened in cocaine users. It is hypothesized that cocaine-induced apoptosis damages the muscular layer of the small vessels or that the damage is once again due to the direct oxidant effect of cocaine.[39] The smaller artery lumen may lead to a mismatch in blood flow supply-demand, and ultimately under perfusion whereby the myocardium is not receiving enough blood and becomes ischemic. Lastly, cocaine users' hearts often resemble those of patients with heart failure secondary to pheochromocytoma. The high levels of catecholamine, particularly norepinepherine, seem to induce a diffuse pattern of discrete fibrotic lesions, which tend to favor reentry and the induction of arrhythmias.[40]

Hypertrophied hearts with diffuse fibrosis and microangiopathy utilize oxygen less efficiently and are more likely to have disordered electrical conduction. During times of increased stress, the myocardium becomes ischemic and should have a lower threshold for fibrillation. Unfortunately, few case series have been able to publish the initial cardiac rhythms found at the scene of cocaine-associated EXD fatalities. One report documents 18 fatal EXD cases with 13 primary cardiac rhythms confirmed by emergency personnel.[6] Only one victim was confirmed to have ventricular tachycardia and none were found to have ventricular fibrillation. If primary arrest was strongly associated with sudden death in excited delirium, it would be expected that more victims would have presented with the above-mentioned abnormal rhythms. However, this case series was limited because the exact time delays in determining initial cardiac rhythms on arrival of emergency medical services to the scene was not available; thus, it is impossible to calculate how many of the patients might have progressed from ventricular tachycardia/fibrillation to asystole. Nevertheless, the molecular, cellular and anatomic alterations induced by chronic higher-dose cocaine use might explain why very low cocaine levels can be lethal in EXD victims.

MANAGEMENT

While our understanding of EXD is expanding, the disorder still presents significant challenges to emergency first responders and physicians. Recent research has demonstrated unique cellular and neurochemical alterations in EXD victims, leading to dopamine excess and autonomic hyperactivity. EXD victims display extreme agitation, aggression, unexpected physical strength and florid psychosis. Emergency physicians must recognize the danger posed by these patients and should act in an expeditious and aggressive manner to avoid medical complications including metabolic acidosis, rhabdomyolysis, hyperthermia, multisystem failure and/or death. To address these clinical findings, we propose a treatment protocol that includes rapid sedation, followed closely by external cooling, intravenous (IV) fluids, monitoring, and treatment of potential medical complications.

Given the violent and unpredictable nature of EXD victims, rapid sedation is likely essential to positive outcomes. Furthermore, if autonomic hyperactivity and aberrant dopamine processing is to blame for the clinical presentation of EXD, then the ideal drug(s) needs to "turn off" the catecholamine cascade and rapidly sedate the patient. Several types of drugs could fulfill these requirements. Neuroleptics, benzodiazepines, or both in combination are commonly used in the management of agitated patients; however, to date, there

are no published double-blind, randomized, placebo-controlled trials to confirm the efficacy and safety of antipsychotic medications to manage acute delirium.[41] One study of 111 violent and agitated patients by Nobay et al[42] compared efficacy and side effect profiles of intramuscular (IM) midazolam (5mg), lorazepam (2mg) and haloperidol (5mg) randomly assigned to the study participants. They concluded that midazolam had a significantly shorter onset (18.3 +/- 14 minutes) and more rapid time to arousal. Several studies found a significant advantage in combining two or more drugs to achieve maximal sedation. For instance, Battaglia et al[43] and Bieniek et al[44] documented superior efficacy and similar side effect profile for a combination haloperidol and lorazepam versus either drug alone.

Despite the proven efficacy and safety record of neuroleptics and benzodiazepines, they require at least 10-15 minutes for sedation. EXD victims may not have minutes to spare as they continue to struggle against law enforcement or physical restraints in a state of hyperthermia and metabolic acidosis. With the particulars of EXD in mind, we propose intramuscular ketamine as an alternative sedating agent worthy of consideration. It is a drug that can be administered IM (4-5 mg/kg/dose; onset of action: 3-4 minutes) or IV (1-2 mg/kg/dose; onset of action: 30 seconds), does not require endotracheal intubation, and reliably produces rapid analgesia, sedation, and amnesia via direct action on the cortex and limbic system. The use of ketamine for procedural sedation in the pediatric ED and rural operating rooms is popular and has a proven record of efficacy and safety.[45] With 25 years surgical experience in the South Pacific, Reich et al[46] documented that ketamine was effectively used to sedate 866 unmonitored patients without serious complications.

Adult data on ketamine use in the ED is sparse, but one recent literature review by Strayer et al[47] attempted to determine ketamine's adverse effect profile when used for procedural sedation. The analysis revealed that IM ketamine reliably produced adequate sedation to facilitate painful procedures with few side effects. Emergence phenomenon was documented in 10-20% of patients; but if ketamine was administered with a rapidly metabolized benzodiazepine (i.e. midazolam), then the effects were reduced significantly. In a unique retrospective study of 11 combative trauma patients, Melamed et al[48] found that sedation with ketamine, with or without midazolam, was effective in all cases. Ketamine was administered intravenously for sedation by prehospital providers during an average transport time of 114 minutes. Although this report is based on a very small sample size, the authors reported no adverse events and suggest that ketamine might be an ideal intervention for the combative patient.

Although concerns about ketamine causing increased intracranial pressure and/or laryngospasm and subsequent airway obstruction have lessened, the agitated EXD victim represents a unique patient group for future analysis of the drug.[45,49] Furthermore, if a catecholamine surge is at least partially responsible for the medical and psychiatric symptoms of EXD victims, then ketamine might actually exacerbate the underlying problem by acting as a mild stimulant of the cardiovascular system.[46] Therefore, ketamine's most lauded characteristic of having no cardiovascular, respiratory or airway protective reflex depression, might also be cause for concern. One could imagine a scenario in which ketamine's rapid and superior sedation might lure the emergency physician into a false sense of security while the EXD patient is quietly decompensating. Perhaps the potential cardiovascular stimulation could be averted by using a β-adrenoreceptor blocker immediately after sedation with ketamine, as suggested by the results of a recent in vitro study using human atrial myocardium.[50] Despite the promise of ketamine, more structured research is needed to establish its safety and efficacy for emergent sedation of the agitated patient.

In addition to adequate sedation, several protective measures must be taken to increase the chances of survival in persons presenting with EXD. Proper management should arrest the catecholamine cascade quickly. Medical evaluation should begin promptly and include basic monitoring (IV access, pulse oximetry and oxygen), radiographs, blood tests and a focused physical exam. As mentioned previously, EXD victims present with autonomic hyperactivity, which often leads to metabolic acidosis, hyperthermia, and rhabdomyolysis. This clinical picture is similar enough to that of malignant hyperthermia (MH) and neuroleptic malignant syndrome (NMS) that dantrolene could be considered as another useful adjunctive therapy. One informative case report described a 25 year old patient with cocaine-excited delirium and severe acidosis who was treated with hyperventilation, passive cooling, sodium bicarbonate and dantrolene.[51] This intervention lead to a swift correction of the acidosis and the patient survived. Dantrolene is a hydantoin derivative that abolishes excitation-contraction coupling of muscle cells by blocking calcium release from intracellular storage in the sacroplasmic reticulum. It has been used successfully for years by anesthesiologists to treat MH and NMS; however, its use in emergent situations is limited by poor water solubility and difficulties in rapidly preparing a suitable solution for IV administration.[52,53]

CONCLUSION

EXD is a unique medical issue characterized by the acute onset of agitation, aggression, distress, and possibly sudden death. While the contribution of restraint, struggle and the use of electrical conduction devices to the cause of death raises controversy, recent research points toward central nervous system dysfunction of dopamine signaling as a cause of the delirium and fatal autonomic dysfunction. Victims of EXD usually die from cardiopulmonary arrest, although the exact cause of such arrest is likely multifactorial and chronic. Unfortunately, an adequate treatment plan has yet

to be established, although rapid sedation, followed closely by external cooling, IV fluids, monitoring, and treatment of potential medical complications is likely critical to decrease morbidity and mortality. Neuroleptics, benzodiazepines and ketamine are among the potent sedating agents that have been proposed to stabilize EXD victims. While there is still much to be discovered about the pathophysiology and treatment, it is hoped that this extensive review will provide both police and medical personnel with the information necessary to recognize and appropriately respond to EXD.

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