



Diagnostic pitfalls and forensic implications of hyperactive delirium with severe agitation: an Italian case series[☆]

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ABSTRACT

Hyperactive Delirium with Severe Agitation (HDSA) is characterized by disorientation and aggressive behavior, constituting an acute, life-threatening medical emergency that requires prompt intervention. It is frequently associated with substance use. In prehospital settings, management often involves physical restraint, force, or pharmacological sedation; however, the diagnostic criteria and medico-legal implications of HDSA remain insufficiently defined. We retrospectively analyzed seven fatal cases exhibiting HDSA presentations, as defined by the American College of Emergency Physicians (ACEP), from the archives of two university-based forensic pathology centers. A detailed multidisciplinary review by forensic pathologists and forensic psychiatrists showed that six of seven decedents were males aged 25 to 36 years who experienced sudden cardiorespiratory arrest during episodes of severe agitation. Four deaths were preceded by law enforcement involvement, and five occurred immediately following attempts at manual restraint, implicating restraint-associated asphyxia as a potentially significant factor in mortality. Toxicological analyses detected psychostimulant exposure in five cases. This study represents, to our knowledge, one of the first to employ the updated HDSA terminology to describe fatal cases within a medico-legal forensic psychiatric context.

1. Introduction

Hyperactive Delirium with Severe Agitation (HDSA) represents a condition of altered mental status distinguished by disordered thinking and psychomotor agitation, often accompanied by a hyperadrenergic state [1]. Although public awareness surged only in the past decade – largely because of high-profile deaths such as those of George Floyd and Elijah McClain – the syndrome has been recognized in forensic and psychiatric literature since the early nineteenth century. Calmeil in 1832 and Maudsley in 1867 first documented episodes of violent psychomotor agitation accompanied by hyperactivity and febrile exhaustion [2]. Soon afterward, Luther Bell's 1849 description of "*acute exhaustive mania*"

detailed institutionalized patients who exhibited behavioral disorganization, hallucinations, fever, and a high mortality rate [3]. Stauder formalized this clinical picture in 1934 as "*lethal catatonia*," stressing its link to sudden death in young, otherwise healthy individuals who displayed violent behavior, hyperthermia, and altered mental states [4]. Psychiatric practice changed dramatically between 1952 and 1975 with the introduction of neuroleptic drugs, whose use reduced the incidence of exhaustive mania even as a surge in cocaine abuse shifted attention to substance-related presentations. Wetli and Fishbain's 1981 report of acute cocaine delirium in a "*body packer*" (an individual smuggling cocaine internally) highlighted this shift [5]. In 1985, the same authors coined the term Excited Delirium Syndrome (ExDS) to describe young

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males who, after using cocaine, exhibited extreme agitation, violence, hyperthermia, and sudden cardiorespiratory collapse. In these cases, police intervention was common, with restraint often preceding death, and autopsies rarely revealed an anatomical cause, effectively ruling out overdose, trauma, or pre-existing cardiac disease [6]. Recognizing both the clinical urgency and diagnostic ambiguity of Excited Delirium Syndrome, the American Academy of Emergency Physicians (ACEP) convened a Task Force in 2009. Its White Paper synthesized potential prehospital indicators, primarily drawn from a Canadian police census of more than one million public encounters. This census identified agitation, increased pain tolerance, sweating, tachypnea, tactile hyperthermia, lack of fatigue, unusual strength, resistance to law-enforcement officers, inappropriate disrobing, and attraction to mirrors or glass as suggestive features when at least six criteria were present [7]. The document emphasized that Excited Delirium Syndrome was already acknowledged by several medical organizations, including the National Association of Medical Examiners, and that variations in terminology should not be construed as evidence against the syndrome's existence [7,8].

Despite ACEP's endorsement of Excited Delirium Syndrome as a distinct condition [7], the American Medical Association and the American Psychiatric Association have refrained from endorsing it, citing a lack of sufficiently specific diagnostic criteria [9,10]. Notably, neither Excited Delirium Syndrome nor its successor term, HDSA, is included in the World Health Organization (WHO)'s ICD-10 or in the DSM-5-TR [11,12]. In its position statement, the APA underscored the absence of rigorous validation studies and pointed out discrepancies between the proposed symptom constellation of HDSA and the DSM-5-TR's definition of hyperactive delirium [9]. As a result, Excited Delirium Syndrome has often been used indiscriminately as a catch-all term for agitated, disoriented patients many of whom are under the influence of psychoactive substances [13]. The 2009 ACEP White Paper revised the terminology to replace the stigmatizing label *Excited Delirium* with a more descriptive, evidence-based approach that incorporates validated agitation scales, ethical and medicolegal considerations, and prioritizes rapid, patient-centered intervention. In 2021, ACEP issued an updated report renaming the condition *Hyperactive Delirium with Severe Agitation* to enhance diagnostic clarity and shift the focus from postmortem characterization to active therapeutic management [1]. By 2023, ACEP formally removed Excited Delirium from its emergency medicine guidelines, while acknowledging its continued use in forensic settings, and affirmed HDSA as the preferred terminology [1,14].

The limitations of diagnosing Excited Delirium Syndrome were also highlighted in a systematic review that examined its definition, epidemiology, and pathophysiology [15]. The review found that the overall quality of the studies was poor and confirmed the lack of a universally recognized definition, as the diagnosis remains primarily syndromic and is based on subjective clinical criteria [15].

Notably, in the United Kingdom, the Independent Office of Police Conduct (IOPC) has removed the term Excited Delirium Syndrome from its investigation reporting forms and announced that it will no longer be used to categorize cases under review. Similarly, several U.S. states, including Colorado and California, have prohibited the use of the term by law enforcement, medical professionals, and coroners [16]. Furthermore, in 2024, the American College of Pathologists (CAP) officially declared that it no longer recognizes "excited delirium" as a valid cause of death [17]. Therefore, the present article therefore adopts the updated terminology proposed by ACEP.

Compounding the confusion, the ACEP descriptions themselves do not explicitly include the core elements of delirium, namely an acute, fluctuating disturbance of consciousness and attention accompanied by perceptual and cognitive changes, features that have long accepted in psychiatric definitions [18].

Several etiological theories have been proposed over the past decades, including excessive dopamine release associated with chronic cocaine use in genetically predisposed individuals. Nevertheless, in

forensic practice no universally accepted standard exists for defining or explaining the underlying mechanisms of HDSA, rendering the condition primarily descriptive [2,19–22].

To date, few articles have adopted the updated HDSA terminology, and only a limited number of cases have been examined through a medico-legal postmortem approach [23,24]. The present work aims to address that gap by presenting a thorough case study with detailed clinical and autopsy findings, aiming to enhance the understanding of HDSA in forensic investigations, promote timely recognition, and inform prevention and intervention strategies in both medical and legal contexts.

2. Materials and methods

We reviewed forensic autopsy reports issued over the past five years by two expert pathologists at the Institute of Legal Medicine of the University of Rome Tor Vergata and the Institute of Legal Medicine of University of Bari "Aldo Moro". These reports, prepared at the request of five separate Italian Public Prosecutor's Offices, were included in the study if their findings aligned with the HDSA presentations as defined by ACEP. Specifically, cases had to show evidence of altered mental state (as disorientation, defects in judgements or thought, and disruptions in perception, psychomotor skills, and behavior) with psychomotor agitation and fatal outcome [1]. From this pool, seven consultations met these criteria and were subjected to detailed review by forensic pathologists and forensic psychiatrists among the study authors.

For each case, we extracted and tabulated the following variables: (i) relevant historical features, (ii) observations at the scene, (iii) initial findings upon first contact, (iv) data from clinical assessment, (v) circumstances and characteristics of death, and (vi) autopsy findings. For detailed breakdown details of the analyzed features, refer to Table 1.

3. Case series

3.1. Case 1

A 30-to-35-year-old male, affected by arterial hypertension and hepatitis C virus (HCV) – related hepatitis, presented with psychomotor agitation and behavioral disturbance characterized by sudden and abrupt mood swings at his residence. After considerable effort, law enforcement personnel managed to persuade him to be transported to a nearby emergency department via ambulance. Upon arrival, the young man briefly exhibited a reduction in agitation but soon became physically aggressive again, necessitating physical restraint and intramuscular administration of chlorpromazine (50 mg), promazine (25 mg), and delorazepam (2 mg). Shortly thereafter, the patient exhibited pulseless electrical activity and experienced cardiorespiratory arrest.

The autopsy revealed non-specific signs of asphyxia death, including subpleural and subepicardial petechiae. Histological examination showed congestion in the brain, lungs, and heart. Toxicological investigations returned negative results for substances of abuse or other potentially contributory agents.

3.2. Case 2

A deceased male, aged 30 to 35, with a history of substance abuse, was found dead in his apartment. The residence was in a significant disarray, with clothes scattered on the floor, furniture displaced, and the bathroom in a state of severe disrepair. Notably, the stall was shattered into multiple fragments, with tiles dislodged. A streak of material, suspected to be blood, was detected along the edge of the bathtub where the body was located.

Upon external examination, the body displayed numerous bruises and abrasions, primarily on the upper and lower limbs, as well as swelling of the right lower limb. The autopsy revealed non-specific findings. Toxicological investigations tested positive for cocaine.

Table 1
Cases analysis by the most frequently reported features in the literature for hyperactive delirium with severe agitation.

	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6	Case 7
Features in History							
Gender	Male	Male	Male	Male	Male	Male	Female
Age	30–35	30–35	25–30	30–35	30–35	40–45	43
Acute onset	YES	no	n.a.	YES	no	n.a.	YES
History of Mental Illness	n.a.	no	n.a.	YES	negative	YES	no
History of Psychostimulant abuse	no	YES	n.a.	no	negative	YES	YES
Features evident at scene							
Call for disturbance	YES	no	YES	no	YES	no	YES
Bizarre behavior	YES	YES	YES	YES	YES	YES	YES
Violent behavior	YES	YES	no	YES	YES	YES	YES
Psychotic symptoms	no	YES	YES	YES	YES	YES	no
Subject Obese	no	YES	YES	no	no	no	YES
weight (Kg); length (cm); BMI (kg/m ²)	w: 73 l: 180 BMI: 22.5	w: 94 l: 173 BMI: 31.4	w: 92.8 l: 173 BMI: 31	w: 98 l: 181 BMI: 29.9	w: 101 l: 186 BMI: 29.2	w: 78 l: 182 BMI: 23.5	w: 112 l: 161.6 BMI: 43.3
Features evident on contact							
Noncompliance with police directives	YES	no	YES	YES	YES	YES	YES
Indefatigability	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.
Constant physical activity	YES	no	YES	no	no	YES	YES
Features with clinical assessment							
Tachypnea	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.
Tachycardia	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.
Hyperthermia	n.a.	n.a.	n.a.	YES	n.a.	n.a.	n.a.
Hypertension	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.
Acidosis	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.
Rhabdomyolysis	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.
Features of death							
Pre-terminal hypoactive phase	YES	n.a.	no	YES	YES	no	no
Sudden collapse after restraint	YES	no	YES	YES	no	YES	no
Respiratory Arrest described	no	no	YES	YES	YES	no	n.a.
Cardiac rhythm brady-asystole or PEA	YES (PEA)	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.
Aggressive resuscitation efforts unsuccessful	YES	no	YES	no	YES	YES	YES
Features on autopsy							
Drug screen Positive for psychostimulants	no	YES	No	YES	YES	YES	YES
Drugs levels lower than anticipated		no		no	no	no	no
No anatomic correlated for death	signs of asphyxia death (subpleural and subpericardial petechiae). Full-mantle hypostasis	signs of asphyxia death (subpleural petechiae; multiorgan congestion)	YES, just poly-visceral congestion	YES, signs of asphyxia death (multiorgan congestion; subpericardial and subserous petechiae; lung oedema). Crumpled plastic films (1 in hypopharynx; 6 in the stomach). Two rolls of tape in the stomach.	signs of asphyxia death (skin petechiae, signs of congestion). Blood in airways.	multiple cut lesions (head, thorax, abdomen) with leakage of abdominal organs. Poly-visceral congestion.	YES hemorrhagic lung oedema, cyanosis of head, lips and hands, multiorgan congestion,

w: weight; l: length; BMI: Body Mass Index.

3.3. Case 3

A man aged 25 to 30 displayed erratic behavior at an airport while attempting to board the flight. The individual bypassed the security checkpoint and accessed the runway trying to board the plane without a boarding pass. Airline staff intervened, preventing him from boarding, but he refused to leave the stairs leading to the plane. Airport police and medical staff were required to restrain him and administer intramuscular diazepam (10 mg) and promazine (25 mg) for sedation. Shortly afterward, the individual experienced respiratory arrest, and despite resuscitative efforts, he could not be revived. A search of his luggage revealed multiple psychotropic drugs, including benzodiazepines and antipsychotics.

The autopsy revealed evidence of poly-visceral congestion, but no specific cause of death was identified. Toxicological investigations returned negative results.

3.4. Case 4

The fourth individual was a male aged 30 to 35 with a history of depressive disorder who had discontinued treatment with antidepressant medications. He had recently experienced a stressful event (the end of a significant romantic relationship) and was living with his father. Later in the evening, after dinner, his father observed the man displaying erratic and non-purposeful behavior, including aimlessly wandering the apartment, throwing objects, speaking incoherently, and displaying aggressive tendencies. After attempts at verbal de-escalation, the father restrained his son in an armchair once the crisis subsided. The young man appeared to fall asleep, exhausted. The following morning, the father discovered his son deceased in the same position in the chair, with a reported high body temperature.

The autopsy revealed poly-visceral congestion, most prominently in the brain, kidneys, and lungs, along with subepicardial and subserosal petechiae. Toxicological investigations returned positive results for cocaine and ethanol.

3.5. Case 5

A male aged 30 to 35 with no known history of chronic illnesses or drug abuse, exhibited erratic and self-injurious behavior in a public square during a period of intense summer heat. Witnesses described the individual as shirtless and barefoot, shouting incoherently and engaging in unusual actions such as rubbing his head and limbs against the hot asphalt. Suddenly, he stood up, began running, and collided with a supermarket door before entering the building. He then collapsed, lying supine while discarding his personal belongings and continuing to shout. Police officers and bystanders attempted at verbal de-escalation unsuccessfully. The man experienced cardiorespiratory arrest, confirmed by paramedics who arrived to attempt resuscitation, but were unsuccessful.

The external post-mortem examination revealed widespread blackish staining on the right side of the abdomen, forearms, hands, and feet on both sides. Additional contusions were noted on the head, eyelids, and limbs. The autopsy revealed dark, bloody fluid in the airways and significant congestion in the leptomeninges and petrous ridges. Toxicological investigations returned positive results for cocaine.

3.6. Case 6

A male, aged 40 to 45, with a history of substance abuse (alcohol, cannabinoids and cocaine) and unspecified personality disorder, suddenly inflicted multiple self-injuries using a folding knife in his apartment, resulting in significant blood loss. After his father called for help, the victim initially left the house, but came back and barricaded himself inside his bedroom. Law enforcement and emergency medical personnel were initially unable to enter, as the man forcefully resisted by holding

the door shut. After several attempts, they gained entry and found the individual agitated, naked, and covered in blood. Management of the episode required a combination of physical restraint, the use of a Taser, and pharmacological intervention, including unspecified intravenous sedatives and anesthetics. Despite these interventions, the state of agitation persisted. The man continued to inflict self-injury, banging his head on the floor, and exhibited aggressive behavior toward the medical personnel on several occasions. Two minutes after receiving intravenous sedatives and anesthetics, the individual experienced cardiopulmonary arrest. Resuscitation efforts were unsuccessful, and he was pronounced dead shortly thereafter.

A post-mortem external examination revealed numerous stab and cut wounds. Notably, five cut wounds appeared on the occipital region, and a stab-and-cut wound was found in the right costal region (second intercostal space). Additionally, three wounds consistent with Taser darts were also present on the victim's body. Toxicological investigations returned positive results for cocaine, ketamine, and cannabinoids.

3.7. Case 7

A woman aged 40 to 45 with a known history of substance abuse obstructed emergency department personnel during the management of a man in a state of acute intoxication. She appeared extremely agitated and displayed both verbal and physical aggression toward the emergency physician. She then boarded the ambulance, actively interfering with the ongoing medical intervention thereby compromising the safety of both the medical team and the patient. After a short time, she seemed to calm down and was persuaded to leave the vehicle. However, just minutes later, she suddenly collapsed and lost consciousness. Despite prompt cardiopulmonary resuscitation attempts by the emergency physician, including the administration of five 1-mg doses of intravenous epinephrine, she was pronounced dead. A forensic inspection of her residence, carried out by police, revealed the presence of cocaine.

The external post-mortem examination showed cyanosis of the face, lips, and hands, along with multiple bruises and ecchymoses on the chest and upper limbs. The decedent was also obese. Autopsy findings included marked visceral congestion involving the brain, cervical vessels, lungs, heart, liver, pancreas, and kidneys. The cerebral sulci appeared mildly effaced, and a focal ecchymosis was observed in the sternocleidomastoid muscle. Signs of pulmonary hemorrhagic edema were also evident. Toxicological analysis confirmed the presence of cocaine and its metabolites in biological samples.

4. Discussion

This case series provides valuable insights into the clinical features and forensic challenges of HDSA, in the context of ACEP's October 2023 statement [14]. Among the seven cases analyzed, six victims were male [25], with five aged between 25 and 36 years, reflecting established epidemiological patterns for ExDS [15].

In nearly half of the cases with adequate documentation, symptoms developed abruptly, which helps to explain why HDSA is most often commonly encountered in high-intensity environments such as pre-hospital emergency medical services [26,27], police interventions [28–30], and forensic settings [7,15]. Only four of the seven cases received medical treatment, highlighting how the rapid escalation of agitation can impede prompt medical intervention in these time-sensitive contexts [7].

A comprehensive assessment of vital signs, including tachypnea, tachycardia, hyperthermia, hypertension, acidosis, and rhabdomyolysis, was not feasible in all cases. Cardiac rhythm was documented only in Case 1, which showed pulseless electrical activity. Differential diagnosis, particularly regarding the possibility of drug-induced arrhythmias such as torsades de pointes, known to occur with antipsychotics [31], especially when combined with cardiotoxic substances like cocaine [32],

remains challenging. The significant lack of systematic cardiac rhythm analysis in most forensic investigations of HDSA cases represents a significant gap, potentially obscuring iatrogenic factors that contribute to mortality. This scarcity of detailed clinical data may stem from the rapid escalation of symptoms, which limits the time available for thorough assessment. Furthermore, it highlights the challenges in early detection and prevention, underscoring the limited opportunities clinicians have for intervention once HDSA develops.

Obesity was noted in three patients, a factor linked to higher HDSA mortality likely due to an exaggerated catecholamine surge [27,33].

Autopsies, in nearly all cases, revealed signs of asphyxia, with no definitive alternative cause of death identified. As a result, HDSA remains a diagnosis of exclusion in forensic practice, relying on thorough review of the decedent's preceding clinical presentation [34–36] and highlighting the current absence of pathognomonic postmortem markers [2,20,37]. The limited clinical information in this and other retrospective series arises from fundamental differences between emergency-medicine and forensic workflows. The ACEP Task Force Report defines HDSA for *in vivo* diagnosis based on observed symptoms to guide management, whereas forensic evaluation occurs *ex post* via retrospective review of often-incomplete law enforcement and medical reports, on-scene findings, and autopsy result [1].

The interpretation of our findings must account for the possible selection bias of medico-legal case series, which predominantly capture fatal outcomes and therefore cannot be generalized to nonfatal HDSA presentations [15]. A further concern especially in U.S. studies is racial bias as Black individuals are disproportionately diagnosed with '*excited delirium*' in fatal law-enforcement encounters [38,39]. The ACEP criteria have previously been criticized for perpetuating stereotypes and relying on subjective signs such as '*increased strength*', reduced pain sensitivity, and '*bizarre behavior*' [38,40]. These broad definitions, combined with the lack of formal recognition of ExDS by leading medical authorities, have hindered the systematic collection of data essential for accurate epidemiological assessments, standardized clinical definitions, and rigorous research. It is anticipated that, following the ACEP's October 2023 statement, research efforts will benefit significantly. Reported fatality rates vary widely – 8.9% in unspecified settings [7], 16.5% in cocaine-related deaths [19], and 11.1–12.5% in cases involving conducted electrical weapons or in-custody deaths [20,28,30], reflecting heterogeneous data and study designs.

HDSA typically arises in contexts of severe agitation necessitating restraint or custodial measures to prevent harm [37]. Uncertainty surrounding HDSA's pathophysiology further limits diagnosis and epidemiological clarity. Most evidence supports a multifactorial origin – involving excessive endogenous catecholamine release from stress response, intense exertion, or psychostimulant use [2,41], with cocaine-induced oxidative stress and dopaminergic dysregulation playing key roles [15]. Genetic predispositions affecting alpha-synuclein, opioid, and dopamine receptors may modulate risk [2,42,43]. Notably, chronic cocaine users show upregulated dopamine transporters [21,44,45], but this adaptation may be absent or reduced in HDSA victims, suggesting a distinct pathway marked by hyperthermia (~40.7 °C) and autonomic storm, culminating in tachyarrhythmias and sudden cardiac arrest [2,3,46]. Hyperactivation of dopaminergic pathways and targeted brain regions (insula, amygdala, and cingulate cortex) may induce sympathetic hyperactivity, resulting in tachycardia, arrhythmias, and potentially culminates in cardiac arrest. At the same time, increased dopaminergic activity could alter respiratory drive and exacerbate the bodies inability to compensate for low oxygen levels, possibly leading to more pronounced effects of hypoxia. [2]. Dysregulated signaling within the brain–heart axis may trigger sudden fatal arrhythmias, as hyperdopaminergic activity in the limbic system can convert intense stress into autonomic dysfunction, even in the absence of structural heart disease [2]. Furthermore, upregulation of the HSPA1B gene, which encodes heat shock protein 70 (Hsp70), has been documented in individuals who died from hyperactive delirium. This molecular evidence

substantiates the contributory role of hyperthermia in the pathophysiology, although HSPA1B expression is not pathognomonic for the syndrome [3].

Individuals with HDSA has been categorized into three primary at-risk groups: (1) substance users, particularly chronic cocaine binge users, who constitute the largest and most vulnerable group (four cases in our series tested positive for stimulants, though negative toxicology does not exclude the presence of novel psychoactive substances) [47]; (2) patients with pre-existing psychiatric disorders worsened by abrupt medication cessation (one case in our series); and (3) individuals with new-onset psychiatric disease (none observed in our series). These subtypes illustrate HDSA's putative heterogeneous mechanisms, yet neurotransmitter studies remain confined to research settings and were not applied in forensic contexts [2].

A comprehensive understanding of HDSA's pathophysiology is crucial for accurate diagnosis and for determining causal or contributory factors in forensic investigations. Ethical and legal questions regarding the liability of law enforcement and healthcare providers arise within the context of limited diagnostic frameworks [33].

Law enforcement officers frequently encounter HDSA patients and may resort to forceful restraint, which is often implicated in fatal outcomes. Restraint positions such as prone or 'hobble' have been associated with asphyxia [27,48–50]. A pooled analysis of 104 fatal cases found aggressive restraint more common in deaths, while survivors more frequently received sedation, suggesting that restraint may amplify, rather than solely cause, fatal outcomes [51]. In our series, law enforcement was involved in four of seven deaths. Scene investigations, including clinical records, witness statements, video, restraint documentation, and medical response timelines, are crucial for reconstructing events and excluding alternative causes in the absence of specific autopsy signs [35,52]. The medico-legal implications of an HDSA diagnosis are particularly complex, as the condition emerges in high-stakes encounters involving law enforcement and emergency medical interventions. This context raises important questions about whether the diagnostic label serves legitimate clinical purposes or functions as a medicolegal construct that may inadvertently shield institutional liability by attributing deaths to what appears to be an unavoidable medical emergency.

Given the potential liability, law enforcement must prioritize risk mitigation through targeted training in early recognition of HDSA, de-escalation techniques, non-lethal restraint methods, and prompt transfer to medical teams. Emergency physicians must ensure not only stabilization but also meticulous documentation and collection of biological samples for toxicological and molecular analyses, despite operational challenges [53,54]. Such data are vital for diagnostic refinement, tracking epidemiological trends, validating biomarkers, and developing future clinical and forensic guidelines. A multidisciplinary approach is indispensable to improve diagnostic precision, guiding best practices, and informing evidence-based policies [33].

These findings reflect broader concerns in the literature regarding the conceptual and diagnostic limitation of HDSA. Our case series illustrates how incomplete data hinder and obstruct the ability to make a definitive diagnosis [7].

5. Conclusion

This case series addresses a significant gap in the literature by providing systematically documented cases of HDSA within a medico-legal and forensic psychiatric context, aligned with ACEP's October 2023 statement and reflecting the shift away from the term "*Excited Delirium Syndrome*." Our findings emphasize the considerable challenges in retrospective diagnosis due to incomplete clinical data and the absence of specific pathological markers, highlighting the limitations of current diagnostic frameworks. These findings underscore the urgent need for standardized criteria, improved collaboration, especially among medico-legal experts, forensic psychiatrists, and emergency

medicine practitioners, and ongoing research to improve diagnostic accuracy and support evidence-based clinical and forensic practice. Furthermore, the evolving terminology necessitates a careful examination of its ethical and legal implications in both forensic and public health domains.

Ethical approval

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Data availability

Data sharing not applicable.

Consent to publish

Not applicable.

CRediT authorship contribution statement

Anna Margari: Writing – original draft, Writing – review & editing, Methodology, Investigation, Data curation, Formal analysis, Visualization. **Alessandro Tavone:** Conceptualization, Investigation, Resources, Data curation. **Andrea Nicola Cardinale:** Writing – original draft, Writing – review & editing, Investigation, Data curation, Formal analysis. **Luigi Buongiorno:** Investigation, Data curation, Formal analysis. **Giulia Petroni:** Data curation, Formal analysis. **Cinzia Niolu:** Methodology, Validation. **Gabriele Mandarelli:** Conceptualization, Methodology, Investigation, Validation, Visualization, Supervision. **Silvestro Mauriello:** Methodology, Resources, Validation. **Francesco Introna:** Methodology, Validation. **Gian Luca Marella:** Methodology, Resources, Validation. **Sara Sablone:** Writing – original draft, Writing – review & editing, Methodology, Investigation, Resources, Validation, Visualization, Project administration.

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References

- [1] B. Hatten, C. Bonney, R. Dunne, S. Hail, G. Ingalsbe, M. Levy, M. Millin, B. Myers, R. Shih, J. Goodloe, ACEP Task Force Report on Hyperactive Delirium with Severe Agitation in Emergency Settings, (2021) 132. <https://www.acep.org/globalassets/new-pdfs/education/acep-task-force-report-on-hyperactive-delirium-final.pdf>.
- [2] D.C. Mash, Excited delirium and sudden death: a syndromal disorder at the extreme end of the neuropsychiatric continuum, *Front. Physiol.* 7 (2016) 435, <https://doi.org/10.3389/fphys.2016.00435>.
- [3] D.C. Mash, L. Duque, J. Pablo, Y. Qin, N. Adi, W.L. Hearn, B.A. Hyma, S.B. Karch, H. Druid, C.V. Wetli, Brain biomarkers for identifying excited delirium as a cause of sudden death, *Forensic Sci. Int.* 190 (2009) e13–e19, <https://doi.org/10.1016/j.forsciint.2009.05.012>.
- [4] K.H. Stauder, Die tödliche Katatonie, *Arch. Psychiatr. Nervenkr.* 102 (1934) 614–634, <https://doi.org/10.1007/BF01813829>.
- [5] D.A. Fishbain, C.V. Wetli, Cocaine intoxication, delirium, and death in a body packer, *Ann. Emerg. Med.* 10 (1981) 531–532, [https://doi.org/10.1016/s0196-0644\(81\)80010-8](https://doi.org/10.1016/s0196-0644(81)80010-8).
- [6] C.V. Wetli, D.A. Fishbain, Cocaine-induced psychosis and sudden death in recreational cocaine users, *J. Forensic Sci.* 30 (1985) 873–880.
- [7] ACEP Excited Delirium Task Force, M. DeBard, J. Adler, W. Bozeman, T. Chan, S. Coffman, M.W. Costello, M.D. Curtis, F. Czarnecki, D. Dawes, C. Hall, J. Heck, S. Henderson, J. Ho, D.C. Mash, M.J. McMullen, J. Metzger, J. Roberts, M. Sztajnkrycer, G. Vilke, American College of Emergency Physicians White Paper Report on Excited Delirium Syndrome, 21 (2009).
- [8] C. Hall, C. Butler, A.S. Kader, S. Palmer, Police use of force, injuries and death: prospective evaluation of outcomes for all police use of force/restraint including conducted energy weapons in a large Canadian city, *Acad. Emerg. Med.* 16 (2009) S198–S199.
- [9] Council on Psychiatry and Law, Position Statement on Concerns About Use of the Term “Excited Delirium” and Appropriate Medical Management in Out-of-Hospital Contexts, APA Off. Actions (2020) 1–2. [https://www.psychiatry.org/File Library/About-APA/Organization-Documents-Policies/Position-Use-of-Term-Excited-Delirium.pdf](https://www.psychiatry.org/File%20Library/About-APA/Organization-Documents-Policies/Position-Use-of-Term-Excited-Delirium.pdf).
- [10] C. Mutchler, New AMA policy opposes “excited delirium” diagnosis, *AMA* (2021). <https://www.ama-assn.org/press-center/press-releases/new-ama-policy-opposes-excited-delirium-diagnosis>.
- [11] W.H.O. (WHO), The ICD-10 classification of mental and behavioural disorders, 1993.
- [12] A.P. Association, Diagnostic and statistical manual of mental disorders, 5th ed, Washington, DC, 2013. 10.1176/appi.books.9780890425596.
- [13] S. Slocum, M. Fiorillo, E. Harding, J. Owen, R. Long, T. Dunn, I. Martin, In pursuit of inter-specialty consensus on excited delirium syndrome: a scoping literature review, *Forensic Sci. Med. Pathol.* 19 (2023) 573–594, <https://doi.org/10.1007/s12024-022-00548-4>.
- [14] ACEP, ACEP Reaffirms Positions on Hyperactive Delirium, (2023). <https://www.acep.org/news/acep-newsroom-articles/aceps-position-on-hyperactive-delirium>.
- [15] P. Gonin, N. Beysard, B. Yersin, P.-N. Carron, Excited delirium: a systematic review, *Acad. Emerg. Med. Off. J. Soc. Acad. Emerg. Med.* 25 (2018) 552–565, <https://doi.org/10.1111/acem.13330>.
- [16] F. Phoebe, B. Arjun, H. Press, Excited Delirium: Why does this discredited term stick around?, (2024). https://www.press.jhu.edu/newsroom/excited-delirium-why-does-discredited-term-stick-around?srsltid=AfmBOorm7eivijlS0LRp_7bmsbR6nyhRr5q2WWkAmoOAS22qx9gwUug.
- [17] C. of A. Pathologists, Why the CAP No Longer Supports “Excited Delirium” as a Cause of Death, (2024). <https://www.cap.org/member-resources/podcasts/why-the-cap-no-longer-supports-excited-delirium-as-a-cause-of-death-january-2024-advocacy-recap>.
- [18] D.A. Brent, J. Max, Psychiatric sequelae of concussions, *Curr. Psychiatry Rep.* 19 (2017) 108, <https://doi.org/10.1007/s11920-017-0862-y>.
- [19] A.J. Rutenber, J. Lawler-Heavner, M. Yin, C.V. Wetli, W.L. Hearn, D.C. Mash, Fatal excited delirium following cocaine use: epidemiologic findings provide new evidence for mechanisms of cocaine toxicity, *J. Forensic Sci.* 42 (1997) 25–31.
- [20] G.M. Vilke, J. Payne-James, S.B. Karch, Excited delirium syndrome (ExDS): redefining an old diagnosis, *J. Forensic Leg. Med.* 19 (2012) 7–11, <https://doi.org/10.1016/j.jflm.2011.10.006>.
- [21] D.C. Mash, J. Pablo, Q. Ouyang, W.L. Hearn, S. Izenwasser, Dopamine transport function is elevated in cocaine users, *J. Neurochem.* 81 (2002) 292–300, <https://doi.org/10.1046/j.1471-4159.2002.00820.x>.
- [22] M.C. Ritz, R.J. Lamb, S.R. Goldberg, M.J. Kuhar, Cocaine receptors on dopamine transporters are related to self-administration of cocaine, *Science* 237 (1987) 1219–1223, <https://doi.org/10.1126/science.2820058>.
- [23] M.J. Casale, L.-Q.-L. MacDonald, A. Mitra, Nutmeg intoxication: a case report, *Cureus* 15 (2023) e46286, <https://doi.org/10.7759/cureus.46286>.
- [24] M.C. O'Brien, K.J. Kelleran, S.J. Burnett, K.A. Hausrath, M.S. Kneer, N. Nan, C.-X. Ma, R.W. McCartin, B.M. Clemency, Fixed dose ketamine for prehospital management of hyperactive delirium with severe agitation, *Am. J. Emerg. Med.* 81 (2024) 10–15, <https://doi.org/10.1016/j.ajem.2024.04.011>.
- [25] S. Sablone, C. Campobasso, C. Tettamanti, A.N. Cardinale, A. Argo, V. Tambone, R. M. Gaudio, R. Cecchi, F. Introna, Gender-based approach: an essential tool in patient safety management and forensic medicine practice, *J. Sex- Gender-Specific Med.* 10 (2024) 167–168, <https://doi.org/10.1723/4343.43288>.
- [26] T.R. Scaggs, D.M. Glass, M.G. Hutchcraft, W.B. Weir, Prehospital ketamine is a safe and effective treatment for excited delirium in a community hospital based EMS system, *Prehosp. Disaster Med.* 31 (2016) 563–569, <https://doi.org/10.1017/S1049023X16000662>.
- [27] S.J. Stratton, C. Rogers, K. Brickett, G. Gruzinski, Factors associated with sudden death of individuals requiring restraint for excited delirium, *Am. J. Emerg. Med.* 19 (2001) 187–191, <https://doi.org/10.1053/ajem.2001.22665>.
- [28] J.R. Grant, P.E. Southall, J. Mealey, S.R. Scott, D.R. Fowler, Excited delirium deaths in custody: past and present, *Am. J. Forensic Med. Pathol.* 30 (2009) 1–5, <https://doi.org/10.1097/PAF.0b013e31818738a0>.
- [29] C.A. Hall, A.S. Kader, A.M. Danielle McHale, L. Stewart, G.H. Fick, G.M. Vilke, Frequency of signs of excited delirium syndrome in subjects undergoing police use of force: Descriptive evaluation of a prospective, consecutive cohort, *J. Forensic Leg. Med.* 20 (2013) 102–107, <https://doi.org/10.1016/j.jflm.2012.05.008>.
- [30] J. Strote, M. Walsh, D. Auerbach, T. Burns, P. Maher, Medical conditions and restraint in patients experiencing excited delirium, *Am. J. Emerg. Med.* 32 (2014) 1093–1096, <https://doi.org/10.1016/j.ajem.2014.05.023>.
- [31] A.H. Glassman, J.T.J. Bigger, Antipsychotic drugs: prolonged QTc interval, torsade de pointes, and sudden death, *Am. J. Psychiatry* 158 (2001) 1774–1782, <https://doi.org/10.1176/appi.ajp.158.11.1774>.
- [32] K. Ryan, P. Benz, A. Zosel, A. Farkas, J. Theobald, QTc prolongation in poison center exposures to CredibleMeds list of substances with “Known Risk of Torsades de Pointes”, *Cardiovasc. Toxicol.* 22 (2022) 866–877, <https://doi.org/10.1007/s12012-022-09764-4>.

- [33] D. Martín-Ayuso, J.J. Pajuelo Castro, A. Santiago-Sáez, B. Herreros, P. Pinto Pastor, Death in custody in Spain: Excited delirium syndrome. Importance of a multidisciplinary approach, *J. Forensic Leg. Med.* 90 (2022) 102393, <https://doi.org/10.1016/j.jflm.2022.102393>.
- [34] S. Kodikara, K. Cunningham, M.S. Pollanen, "Excited delirium syndrome": is it a cause of death? *Leg. Med. (Tokyo)* 14 (2012) 252–254, <https://doi.org/10.1016/j.legalmed.2012.04.003>.
- [35] S.N. Kunz, S. Þórðardóttir, R. Rúnarsdóttir, Restraint-related asphyxia on the basis of a drug-induced excited delirium, *Forensic Sci. Int.* 288 (2018) e5–e9, <https://doi.org/10.1016/j.forsciint.2018.04.051>.
- [36] O. Śliwicka, K. Szatner, A. Borowska-Solonyanko, Three postmortem case reports of the excited delirium syndrome - a short comparison, *J. Forensic Leg. Med.* 66 (2019) 134–137, <https://doi.org/10.1016/j.jflm.2019.06.013>.
- [37] J.R. Gill, The syndrome of excited delirium, *Forensic Sci. Med. Pathol.* 10 (2014) 223–228, <https://doi.org/10.1007/s12024-014-9530-2>.
- [38] B.M. Walsh, I.K. Agboola, E.J. Coupet, J.S. Rozel, A.H. Wong, Revisiting "Excited Delirium": does the diagnosis reflect and promote racial bias? *West J Emerg Med* 24 (2023) 152–159, <https://doi.org/10.5811/westjem.2022.10.56478>.
- [39] A. Saadi, J. Naples-Mitchell, B. da Silva Bhatia, M. Heisler, End the use of "excited delirium" as a cause of death in police custody, *Lancet (London, England)* 399 (2022) 1028–1030, [https://doi.org/10.1016/S0140-6736\(22\)00410-X](https://doi.org/10.1016/S0140-6736(22)00410-X).
- [40] K. Fiscella, D.A. Pinals, C.G. Shields, "Excited delirium," erroneous concepts, dehumanizing language, false narratives, and threat to Black lives, *Acad. Emerg. Med. Off. J. Soc. Acad. Emerg. Med* 29 (2022) 911–913, <https://doi.org/10.1111/acem.14483>.
- [41] J.K. Staley, R.B. Rothman, K.C. Rice, J. Partilla, D.C. Mash, Kappa2 opioid receptors in limbic areas of the human brain are upregulated by cocaine in fatal overdose victims, *J. Neurosci. Off. J. Soc. Neurosci.* 17 (1997) 8225–8233, <https://doi.org/10.1523/JNEUROSCI.17-21-08225.1997>.
- [42] D.C. Mash, Q. Ouyang, J. Pablo, M. Basile, S. Izenwasser, A. Lieberman, R.J. Perrin, Cocaine abusers have an overexpression of alpha-synuclein in dopamine neurons, *J. Neurosci. Off. J. Soc. Neurosci.* 23 (2003) 2564–2571, <https://doi.org/10.1523/JNEUROSCI.23-07-02564.2003>.
- [43] S. Schiavone, M. Neri, E. Mhillaj, C. Pomara, L. Trabace, E. Turillazzi, The role of the NADPH oxidase derived brain oxidative stress in the cocaine-related death associated with excited delirium: a literature review, *Toxicol. Lett.* 258 (2016) 29–35, <https://doi.org/10.1016/j.toxlet.2016.06.002>.
- [44] K.Y. Little, L. Zhang, T. Desmond, K.A. Frey, G.W. Dalack, B.J. Cassin, Striatal dopaminergic abnormalities in human cocaine users, *Am. J. Psych.* 156 (1999) 238–245, <https://doi.org/10.1176/ajp.156.2.238>.
- [45] J.K. Staley, W.L. Hearn, A.J. Rutenber, C.V. Wetli, D.C. Mash, High affinity cocaine recognition sites on the dopamine transporter are elevated in fatal cocaine overdose victims, *J. Pharmacol. Exp. Ther.* 271 (1994) 1678–1685.
- [46] D. Laur, Excited delirium and its correlation to sudden and unexpected death proximal to restraint, in: 2005. <https://api.semanticscholar.org/CorpusID:68074912>.
- [47] R. Barone, G. Pelletti, A. Giorgetti, S. Mohamed, J.P. Pascali, S. Sablone, F. Introna, S. Pelotti, Validation and application of a method for the quantification of 137 drugs of abuse and new psychoactive substances in hair, *J. Pharm. Biomed. Anal.* 243 (2024) 116054, <https://doi.org/10.1016/j.jpba.2024.116054>.
- [48] R.L. O'Halloran, L.V. Lewman, Restraint asphyxiation in excited delirium, *Am. J. Forensic Med. Pathol.* 14 (1993) 289–295, <https://doi.org/10.1097/00004433-199312000-00004>.
- [49] D. Abdon-Beckman, An awkward position: restraints and sudden death., *JEMS* 22 (1997) 88–90,92,94.
- [50] A. Steinberg, Prone restraint cardiac arrest: a comprehensive review of the scientific literature and an explanation of the physiology, *Med. Sci. Law* 61 (2021) 215–226, <https://doi.org/10.1177/0025802420988370>.
- [51] E.M.F. Strömmer, W. Leith, M.P. Zeegers, M.D. Freeman, The role of restraint in fatal excited delirium: a research synthesis and pooled analysis, *Forensic Sci. Med. Pathol.* 16 (2020) 680–692, <https://doi.org/10.1007/s12024-020-00291-8>.
- [52] R. Española, D.M. Legal, A. Pujol-robinat, M. Salas-guerrero, Spanish Journal of Legal Medicine Sudden cardiac death in special circumstances &, *Spanish, J. Leg. Med.* 44 (2018) 38–45, <https://doi.org/10.1016/j.remle.2017.10.001>.
- [53] R. Cecchi, A. Lazzaro, M. Catanese, G. Mandarelli, S. Ferracuti, Fatal thromboembolism following physical restraint in a patient with schizophrenia, *Int. J. Legal Med.* 126 (2012) 477–482, <https://doi.org/10.1007/s00414-012-0670-1>.
- [54] X.A.K. Kersting, S. Hirsch, T. Steinert, Physical harm and death in the context of coercive measures in psychiatric patients: a systematic review, *Front. Psych.* 10 (2019) 400, <https://doi.org/10.3389/fpsy.2019.00400>.