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Refractory Status Epilepticus, Serotonin Syndrome, and Fulminant Multiorgan Failure Following Synthetic Cannabinoid Vaping: A Case Report

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Abstract

Synthetic cannabinoids (SCs) are increasingly prevalent novel psychoactive substances associated with severe, unpredictable and potentially life-threatening toxicity. Although serotonin syndrome following SC exposure has rarely been reported, acute serotonin syndrome diagnosed during the acute phase of SC intoxication has not previously been described. A previously healthy 17-year-old male presented with refractory status epilepticus shortly after inhaling a SC-containing vape. Following withdrawal of sedation, the patient fulfilled the Hunter Serotonin Toxicity Criteria, supporting the diagnosis of serotonin syndrome. The clinical course was complicated by fulminant multiorgan toxicity, including cardiogenic shock requiring veno-arterial extracorporeal membrane oxygenation (VA-ECMO), acute kidney injury requiring continuous renal replacement therapy, severe rhabdomyolysis, persistent hypoglycemia, and ischemic stroke. Routine urine toxicology screening was negative. Following prolonged supportive treatment, the patient made a complete neurological and functional recovery. This case highlights that SC intoxication may present with refractory status epilepticus, serotonin syndrome, and fulminant multiorgan failure despite negative routine toxicology screening. Early clinical recognition, close monitoring, and prompt supportive management are essential, as no specific antidote is currently available.

Keywords

Synthetic Cannabinoids, Serotonin Syndrome, Status Epilepticus, Multiorgan Failure, Vaping

1. Introduction

Synthetic cannabinoids (SCs) comprise a heterogeneous group of laboratory-synthesized compounds designed to mimic and often enhance the psychoactive effects of naturally occurring cannabinoids. Since their emergence in the early 2000s, SCs have gained widespread popularity as novel psychoactive substances (NPS), frequently marketed as "legal highs" or "designer drugs" under street names such as Spice, K2, and Black Mamba [1] [2].

Over the past decade, SC use has increased substantially, particularly among adolescents and young adults. In contrast to Δ9-tetrahydrocannabinol (THC), most SCs act as full agonists at the cannabinoid CB1 receptor, resulting in greater potency and an increased risk of severe toxicity [3]-[5]. Moreover, their chemical structures differ substantially from those of naturally occurring cannabinoids, rendering them undetectable by routine toxicological screening [1] [2] [5]. The continual introduction of novel SC analogues, often through minor structural modifications designed to circumvent both legislative restrictions and analytical detection methods, further complicates their identification and regulation [5]. Consequently, SCs remain particularly attractive to users seeking to avoid detection during conventional drug screening.

Initially, SCs were predominantly dissolved and sprayed onto dried herbal material for smoking [5] [6]. However, with the rapid rise of electronic nicotine delivery systems, they are increasingly marketed as refill liquids for electronic cigarettes and disposable vaping devices. These products are widely available through online retailers and local convenience stores, and their growing popularity on social media platforms has contributed to a marked increase in SC vaping, particularly among teenagers and young adults [3] [4].

Although many users perceive SCs as safe alternatives to natural cannabis, an expanding body of evidence demonstrates that they are associated with a broad spectrum of potentially life-threatening adverse effects, including severe neuropsychiatric manifestations, cardiovascular toxicity, acute kidney injury, rhabdomyolysis, and multiorgan failure [1] [2] [7]. Serotonin syndrome secondary to SC exposure has only rarely been described in the literature. We report the case of a previously healthy adolescent who developed refractory status epilepticus followed by serotonin syndrome and fulminant multiorgan failure after inhalation of a SC-containing vape.

2. Case Description

A previously healthy 17-year-old male was brought to the emergency department by prehospital emergency medical services after experiencing a first generalized tonic-clonic seizure shortly after inhaling a reported Spice vape marketed as containing SCs. According to an eyewitness, the patient had inhaled from the vape shortly before symptom onset, and the witness subsequently provided a photograph of the device, consistent with a commercially available Spice vape marketed as containing SCs. Following recovery, the patient also confirmed using the re-

ported Spice vape immediately before symptom onset. The vape liquid was unavailable for confirmatory toxicological analysis. The patient's parents reported no history of prescribed medication, including serotonergic agents, or dietary supplement use. After recovery, the patient reported occasional cannabis use in the past but denied the use of any other recreational substances or any potential co-exposures, including on the day of presentation.

The initial seizure had terminated spontaneously before the arrival of the pre-hospital emergency medical services. Shortly after their arrival, and before regaining full consciousness, he developed a second generalized tonic-clonic seizure. An intravenous bolus of midazolam was administered immediately after seizure onset, followed by a second bolus five minutes later because of persistent seizure activity. Shortly thereafter, recurrent vomiting increased the risk of aspiration, prompting rapid sequence induction with propofol and rocuronium, followed by endotracheal intubation.

Upon arrival at the emergency department, the patient remained intubated and mechanically ventilated. Initial vital signs revealed an oxygen saturation of 100% while receiving a fraction of inspired oxygen (FiO_2) of 1.0, blood pressure of 177/107 mmHg, heart rate of 99 beats/min, and a body temperature of 36.6˚C, with marked diaphoresis. Neurological examination demonstrated bilaterally dilated but equal and reactive pupils and a decerebrate motor response to painful stimuli (Glasgow Coma Scale score E1M2V1).

Shortly after arrival, recurrent clonic movements developed despite ongoing sedation. A further intravenous bolus of midazolam was administered immediately, followed by a second bolus five minutes later. Intravenous levetiracetam was administered concurrently with the second midazolam bolus, followed ten minutes later by sodium valproate and ketamine. As the clonic movements persisted, continuous propofol and midazolam infusions were further increased ten minutes later, after which no further clinical seizure activity was observed.

Arterial blood gas analysis demonstrated a severe metabolic acidosis with a pH of 7.162, partial pressure of carbon dioxide ($PaCO_2$) of 37.0 mmHg, bicarbonate concentration of 13.0 mmol/L, and lactate level of 9.60 mmol/L. The remaining laboratory parameters on admission were unremarkable.

The admission electrocardiogram showed normal sinus rhythm without abnormalities. Computed tomography of the brain revealed no acute intracranial pathology. Routine urine toxicology screening was negative for amphetamines, methamphetamine, cocaine, opioids, methadone, tricyclic antidepressants, and cannabinoids.

The patient was subsequently transferred to the intensive care unit of a tertiary university hospital for further treatment and monitoring. Owing to logistical constraints, continuous electroencephalography was initiated only during the first attempt to discontinue sedation the following morning rather than immediately upon arrival. During this first attempt to discontinue sedation, after no further clinical seizure activity had been observed, he developed coarse, non-rhythmic

tremors and generalized spontaneous clonus associated with marked limb rigidity and hypertonia. Continuous electroencephalography, initiated during the first attempt to discontinue sedation, demonstrated no ongoing electrographic seizure activity. In the absence of ongoing seizures, the patient fulfilled the Hunter Serotonin Toxicity Criteria by the presence of spontaneous clonus, diaphoresis, and hypertonia, establishing the diagnosis of serotonin syndrome.

During the following days, the patient developed progressive multiple organ failure. He developed anuric acute kidney injury secondary to acute tubular necrosis, with serum creatinine rising to 9.80 mg/dL, necessitating continuous veno-venous hemofiltration (CVVH). In addition, he developed refractory cardiogenic shock with profound hypotension requiring veno-arterial extracorporeal membrane oxygenation (VA-ECMO). Electrocardiography demonstrated anterolateral ST-segment elevation; however, coronary angiography revealed no significant coronary artery disease. Transthoracic echocardiography demonstrated severe global left and right ventricular systolic dysfunction that was not confined to a specific coronary artery territory, accompanied by left ventricular hypertrophy and myocardial oedema, while endomyocardial biopsy revealed mild interstitial lymphocytic infiltrates. The clinical course was further complicated by severe rhabdomyolysis, which developed progressively over the subsequent days after resolution of the clinical seizure activity, with a peak creatine kinase concentration of 168,000 U/L, and persistent hypoglycemia requiring continuous intravenous infusion of 20% glucose.

After five days, hemodynamic support could be gradually weaned, with sufficient recovery of cardiac function to allow successful decannulation from VA-ECMO. Following discontinuation of sedation, the patient regained consciousness and was noted to have ophthalmoplegia. Brain magnetic resonance imaging subsequently demonstrated an acute ischemic infarction involving the left putamen.

The patient remained in the intensive care unit for a total of 21 days and was discharged after an overall hospital stay of 31 days. At follow-up, he had made a complete neurological and functional recovery.

3. Discussion

This case highlights several uncommon manifestations of SC toxicity occurring in a single previously healthy adolescent, including refractory status epilepticus, serotonin syndrome, fulminant cardiogenic shock requiring VA-ECMO, acute kidney failure requiring renal replacement therapy, severe rhabdomyolysis, persistent hypoglycemia, and ischemic stroke. While each of these complications has individually been reported following SC exposure, their simultaneous occurrence is exceedingly rare.

To our knowledge, this is the first reported case of acute serotonin syndrome developing immediately after SC inhalation. Although Khpal and Manning previously reported a case of serotonin syndrome following SC exposure, symptom onset occurred approximately three weeks after exposure, making the temporal as-

sociation less convincing [8]. Therefore, the evidence linking SCs to serotonin syndrome remains extremely limited.

In our patient, persistent epileptic activity was excluded by continuous electroencephalography following withdrawal of sedation. The subsequent development of spontaneous clonus, marked rigidity, tremor, diaphoresis, and agitation fulfilled the Hunter Serotonin Toxicity Criteria, supporting the diagnosis of serotonin syndrome rather than ongoing status epilepticus [9]. The exact pathophysiological mechanism by which SCs may induce serotonin syndrome remains unclear. It has been hypothesized that certain indole-derived SCs may possess serotonergic properties, although this hypothesis is supported by only limited evidence [10]. Experimental studies and case reports have demonstrated interactions between naturally occurring cannabinoids and the serotonergic system, suggesting biological plausibility for a similar effect of SCs [11]-[14]. However, because SCs differ substantially from naturally occurring cannabinoids in both chemical structure and pharmacological profile, these findings cannot be directly extrapolated to SCs, and direct experimental evidence demonstrating serotonergic activity of SCs is currently lacking. Therefore, the proposed mechanisms remain speculative, and further experimental and clinical studies are required to establish a causal relationship between SC exposure and serotonin toxicity.

Beyond serotonin syndrome, our patient developed fulminant multiorgan dysfunction involving the neurological, cardiovascular, renal, and metabolic systems. The broad spectrum of organ involvement likely reflects the widespread distribution of CB1 receptors throughout the body combined with the high potency of SCs [1]-[4]. Nevertheless, the subsequent clinical course was probably multifactorial. While SC toxicity likely played a central role, secondary pathophysiological processes and intensive care interventions may also have contributed to the development of individual organ complications.

3.1. Multiorgan Toxicity

Our patient initially presented with refractory status epilepticus, one of the most severe neurological manifestations of SC intoxication. Although the exact mechanism underlying the proconvulsant effects of SCs remains incompletely understood, experimental studies suggest that, unlike THC, certain SCs produce profound inhibition of GABAergic neurotransmission without a compensatory reduction in glutamatergic activity, resulting in a net proconvulsant effect [1] [7] [15]. Our patient subsequently developed an acute ischemic stroke involving the left putamen, another neurological complication previously described following SC exposure [2] [3] [7] [16] [17]. Although the underlying mechanism remains uncertain, proposed mechanisms include reversible cerebral vasoconstriction, cardiac embolism secondary to arrhythmias, platelet dysfunction, and marked autonomic blood pressure fluctuations [16] [18] [19]. In the present case, however, the ischemic stroke was potentially multifactorial, as profound cardiogenic shock and VA-ECMO support may also have contributed to its development.

Our patient also developed fulminant cardiogenic shock requiring VA-ECMO. Cardiovascular toxicity is increasingly recognized following SC exposure and ranges from tachyarrhythmias and myocardial infarction to severe myocardial dysfunction and cardiogenic shock [1] [7]. Although the exact mechanism remains unclear, activation of cardiac cannabinoid receptors with subsequent disturbances in intracellular ion homeostasis has been proposed [7].

Acute kidney injury is another well-recognized complication of SC intoxication, with acute tubular necrosis being the predominant histopathological finding, consistent with our patient's renal biopsy [4]. Experimental studies suggest that activation of renal cannabinoid receptors may induce mitochondrial dysfunction and tubular cell apoptosis, although these mechanisms have yet to be confirmed clinically [20]. However, in our patient, acute kidney injury was potentially multifactorial, as prolonged hypotension during cardiogenic shock and severe rhabdomyolysis may also have contributed to its development. Severe rhabdomyolysis frequently accompanies SC intoxication and is commonly attributed to seizures or agitation; however, cases occurring in the absence of these factors suggest that direct myotoxicity may also contribute [1]. In our patient, the severe rhabdomyolysis was likely multifactorial. Status epilepticus may have contributed to the initial muscle injury, while sustained muscle rigidity associated with serotonin syndrome, direct SC-induced myotoxicity, and tissue hypoperfusion during cardiogenic shock likely further aggravated muscle damage. Finally, persistent hypoglycemia has only rarely been reported following SC intoxication, and its underlying mechanism remains unknown [21].

3.2. Clinical Implications

Routine toxicology screening does not detect most currently circulating SCs [1] [2] [5]. Consequently, SC intoxication remains primarily a clinical diagnosis and should be considered in adolescents presenting with otherwise unexplained refractory seizures, serotonin syndrome, or multiorgan dysfunction despite a negative toxicology screen. Given the potential for rapid clinical deterioration, early recognition, close monitoring, and timely transfer to a tertiary care center should be considered in patients with severe intoxication. As no specific antidote is currently available, management remains largely supportive and should be tailored to the affected organ systems [2] [17].

3.3. Limitations

This case has two important limitations. Confirmatory toxicological analysis of the vape liquid for SCs was not available. Therefore, the specific SC compound could not be identified. In addition, although the temporal relationship strongly supports SC intoxication as the precipitating event, the precise mechanisms underlying some individual organ complications remain uncertain and were likely multifactorial.

4. Conclusion

In conclusion, this case highlights that SC intoxication may present with refractory status epilepticus, serotonin syndrome and fulminant multiorgan failure despite negative routine toxicology screening, emphasizing the importance of early clinical recognition, prompt supportive management and timely referral to a tertiary care center.

Author Contributions

Senne Van den Bempt conceived the study, collected and interpreted the clinical data, performed the literature review, drafted the manuscript, critically revised the manuscript, and approved the final version.

Conflicts of Interest

The author declares no conflicts of interest regarding the publication of this paper.

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