

Cannabinoid Intoxication in Children: A Challenge in Pediatric Age

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Abstract

Cannabinoid intoxication is rare among the paediatric age, and a high level of suspicion is crucial for the diagnosis. We report two cases of paediatric cannabinoid intoxication that presented with neurologic manifestations (seizure and altered consciousness). Urine toxicological screening was positive for cannabinoids in both cases. The clinical outcome was good with complete recovery, and both children and families were referred for social services evaluation and social risk paediatric consultation. Cannabinoid intoxication should be considered in previously healthy children with acute neurological signs of unknown cause, while also avoiding unnecessary invasive and expensive exams.

Keywords: Cannabinoids/poisoning; Infant; Marijuana Abuse/diagnosis; Parents; Substance Abuse Detection; Substance-Related Disorders

Introduction

Cannabis sativa is the source of different psychotropic drugs: marijuana obtained from flowers, seeds and stems as well as hashish obtained from its resin. The main psychoactive component of *Cannabis* is tetrahydrocannabinol, one of many cannabinoids present in the plant. The tetrahydrocannabinol content is higher in hashish (20%) than in marijuana (5%).^{1,2} The term cannabinoid may also comprise all the ligands of the cannabinoid receptor, including a large number of synthetic cannabinoid analogues.³ The synthetic compound is usually added to herbal products in a highly variable amount. Synthetic cannabinoid analogues are nowadays considered a public health concern due not only to their increasing use but also to their unpredictable toxicity.^{4,5} Cannabinoid intoxication in children is an uncommon and usually accidental event. In Portugal, *cannabis* has been the most consumed illicit drug, with a 9.4% prevalence.^{6,7} With the growing number of consumers

there has also been an increase of case reports of acute *Cannabis* intoxication in children.^{2,8-12}

Consumers mostly use the inhalation route, whereas intoxication in children mainly occurs after accidental ingestion. After the inhalation of marijuana smoke, tetrahydrocannabinol reaches a maximum plasma concentration within minutes, psychotropic effects start within seconds to a few minutes and reach a maximum after 15-30 minutes. The effects start to decrease after 2-3 hours. The effects of tetrahydrocannabinol are delayed when taken orally. The drug is less absorbed and in a more erratic way. Onset is usually 30-60 minutes after ingestion, reaching maximum effect after 2-3 hours.^{3,13,14} The effects of tetrahydrocannabinol, which is a lipophilic compound that has about 20-30 hours half-life may persist for as long as 24 hours, depending on the ingested agent, dose and specific effect.^{3,10}

The diagnosis of *Cannabis* intoxication is made by detecting hepatic degradation metabolites in urine tests.⁹ They may be detectable in urine for up to 12 days, usually for 3-5 days.^{3,14}

In children, the main signs of cannabinoid intoxication are neurological and include prostration, hypotonia, hyporeflexia, hyperkinesia, ataxia, mood changes, seizures and coma.^{2,13,15} Other possible symptoms are nausea/vomiting, conjunctival hyperaemia, dry mouth, tremor, tachycardia or bradypnea/apnea.¹⁵ Although mydriasis is frequent (77%), it might not be present.⁸ Having in mind the high *Cannabis* use amongst today societies, it is mandatory to consider an acute accidental intoxication when a child shows acute neurological signs.

We report two cases of acute *Cannabis* intoxication in children, one of which with misleading presentation.

Case Report

Case Report 1

Sixteen-month old boy, previously healthy, brought to the emergency department with prostration but reac-

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tive to stimuli (modified Glasgow coma score for infants of 13), with one hour of duration and preceded by a two-minute generalised hypertonia and eye revulsion episode. There was no history of fever, no ongoing respiratory or gastrointestinal symptoms and no known trauma. The parents also denied the possibility of accidental ingestion of medications or drugs.

On admission, he was haemodynamically stable, hyporeactive to voice and touch, afebrile and had no signs of trauma. There was no *meningismus*, pupils were isochoric and isoreactive to light, with no focal neurological deficits or other alterations on physical examination. The blood samples - complete blood count, electrolytes, glucose, renal function, transaminases, C-reactive protein and blood gases - were normal, except for the mild hyponatraemia (131 mmol/L). Urine toxicological screening was positive for cannabinoids and negative for benzodiazepines, cocaine, opiates, amphetamines and barbiturates.

He was admitted for monitoring and intravenous hydration and over the following eight hours he fully recovered. While in the hospital, the carer admitted that, the night before, the child had been at a family member's home who was a known *Cannabis* user. He was discharged after child protection services were contacted and he is currently attending regular social risk paediatric assessment.

Case Report 2

Thirteen-month girl, with unremarkable medical history, was brought to the emergency department with altered consciousness described as somnolence, hypotonia (incapable of head control), and a "blank stare". This had started four hours earlier. There was no history of head trauma or administration of medication. She had an afebrile upper respiratory tract viral infection and diarrhoea in the previous three days.

At admission, she was haemodynamically stable and febrile (38.9°C, tympanic temperature). She was somnolent, hypotonic and had dysmetria and slow symmetrical limb movements. Her pupils were isochoric and isoreactive and occasionally she had mastication-like oral movements and a blank look. The rest of the exam was normal, with no meningeal signs.

Considering the possibility of a seizure, she was given 5 mg of rectal diazepam, after which the oral movements ceased. Blood tests were conducted (with vigorous crying from the needle puncture) and complete blood count, electrolytes, glucose, renal function, transaminases and blood gases were all normal, with C-reactive protein of 0.5 mg/L. Head computed tomography (CT) without contrast was normal. Urine toxicology was sent

and returned positive for cannabinoids and negative for benzodiazepines, cocaine, opiates, amphetamines and barbiturates.

She was admitted for monitoring and hydration. Although the carers denied contact with the drug, they were tested and the father was also positive for cannabinoids. The child recovered over the following 24 hours and discharged after a social services evaluation. Currently, the family is attending regular social risk paediatric assessment.

Discussion

We described two acute *Cannabis* intoxication cases, both with neurologic manifestations, which are the most common presenting feature in the paediatric age group. There are two known cannabinoid receptors, type 1 and type 2 cannabinoid receptors (CB1 and CB2). Neurologic symptoms are the result of the stimulation of CB1 located in the brain, in areas such as the basal ganglia, *substantia nigra*, *cerebellum*, *hippocampus* and cerebral cortex.¹⁵ These cases show how the presentation might be easily misinterpreted as postictal, encephalitic or septic, especially when there is also an infectious disease, which is rather common in this age group. In case 2, the fever was a confounding factor, and clinical suspicion was essential for diagnosis.

In a previously healthy child with sudden altered consciousness, seizures, focal neurologic signs or coma, especially if afebrile (although the presence of fever does not exclude this aetiology), one should perform a toxicological screening.^{2,11,13} The differential diagnosis also includes a central nervous system infection, trauma, metabolic abnormalities or stroke.

In case 1, there was hyponatraemia, which is one of the blood abnormalities described in cannabinoid intoxication. This side effect may be explained by the direct effect of tetrahydrocannabinol on the hypothalamic-pituitary axis (vasopressin release) or the effect of an adulterant (for example, methamphetamine).¹³ The results were negative for methamphetamine screening in both our cases.

Toxicological screening might avoid costly and invasive diagnostic tests (like head CT or lumbar puncture) and unnecessary empirical therapy.^{2,12,13} The screening method used in these cases (Nal Von Minden Drug-Screen®) had a cut-off of 50 ng/mL for tetrahydrocannabinol. This toxicological screening also excluded co-intoxication with other substances such as benzodiazepines, cocaine, opiates, barbiturates and amphetamines.

False positives might occur when drugs like efavirenz, proton pump inhibitors, niflumic acid and non-steroid anti-inflammatory drugs are taken.^{12,13,15} In these cases, none of these drugs were administered.

Time of contact with the drug was not fully established but, as described hereinabove, the *Cannabis* metabolites persist in urine for several days and symptoms may persist as long as 24 hours, depending on the amount and tetrahydrocannabinol concentration in the product. A family evaluation is mandatory as well as recreational habits and caregivers usual medications. Yet, very often, drug consumption is denied.^{11,12}

Most of intoxicated children only need supportive care. Benzodiazepines might be an option in agitation states.¹² Case reports have described the use of dexmedetomidine (α -adrenergic agonist) in controlling aggressiveness and agitation, with the advantage of having no effect in the respiratory drive which is typical of other sedatives, thereby avoiding the need for ventilator support.¹⁰

Admission for a minimum period of six hours after ingestion is mandatory, especially for monitoring respiratory function, but if the child is symptomatic, the monitoring period should be at least 24 hours because of the long half-life of tetrahydrocannabinol.^{3,8,10,12,13,15,16}

Most cases have a good prognosis with complete symptom resolution in a few hours, like it happened in these cases.^{2,8,12}

However, there are more severe cases described with seizures, airway obstruction and coma, with the need for admission in an intensive care unit.^{2,8,10} Some authors report an increase in severe presentations due to changes in *Cannabis* product with increased tetrahydrocannabinol concentrations in both marijuana and hashish.¹¹ Another possible explanation for more severe symptoms are adulterants in *Cannabis* resin (anticholinergic substances, cocaine or methamphetamines).^{8,9} In addition, synthetic cannabinoid analogues are more frequently associated with pronounced psychoactive effects, dystonia and seizures.⁹ The routine urine screening for cannabinoids will typically be negative after synthetic cannabinoid analogues consumption because they have different structures from tetrahydrocannabinol.^{4,5} Therefore, whenever the clinical presentation is unusual or severe, the use of other tests should be considered, such as mass spectrometry and gas chromatog-

raphy.^{4,5,13} More than 20 different synthetic cannabinoid analogues structures have been identified, and new ones continue to be synthesised, making its investigation a constant challenge.⁴

Some data from the literature suggest that there is an increased risk for lasting consequences on cognition and neuropsychiatric disorders from cannabinoid exposure in young people.^{12,17} The still-developing brain is more susceptible to the effects of *Cannabis* use, especially when maintained (as it often occurs in adolescents) and increases the risk of further illegal drug intake and the likelihood of *Cannabis* dependence.¹⁸⁻²¹

Even when accidental, cannabinoid intoxication represents a warning sign for the social environment, as it results from inadequate parental or carer supervision. These families should be referred to social risk assessment, in order to prevent and detect cases of neglect/maltreatment.^{2,11,13,18}

WHAT THIS CASE REPORT ADDS

- Cannabinoid intoxication is a rare but increasing issue that should be considered in previously healthy children with acute neurological signs of unknown cause.
- Suspicion is crucial, even when carers deny the possibility of intoxication, and a fever should not exclude the possibility of cannabinoid intoxication.
- Toxicological testing is a non-invasive exam that might avoid using more invasive and expensive exams.
- Social risk assessment/social service referral is mandatory.

Conflicts of Interest

The authors declare that there were no conflicts of interest in conducting this work.

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Protection of human and animal subjects

The authors declare that the procedures followed were in accordance with the regulations of the relevant clinical research ethics committee and with those of the Code of Ethics of the World Medical Association (Declaration of Helsinki).

Confidentiality of data

The authors declare that they have followed the protocols of their work centre on the publication of patient data.

Awards and presentations

Case Report 1 was presented at the 18th National Congress of Paediatrics that took place between 25th and 27th October 2017, Oporto, Portugal.

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