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Case Report

Sudden unexpected death under acute influence of cannabis

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ABSTRACT

The acute toxicity of cannabinoids is said to be low and there is little public awareness of the potentially hazardous cardiovascular effects of cannabis, e.g. marked increase in heart rate or supine blood pressure. We describe the cases of two young, putative healthy men who died unexpectedly under the acute influence of cannabinoids. To our knowledge, these are the first cases of suspected fatal cannabis intoxications where full postmortem investigations, including autopsy, toxicological, histological, immunohistochemical and genetical examinations, were carried out. The results of these examinations are presented. After exclusion of other causes of death we assume that the young men experienced fatal cardiovascular complications evoked by smoking cannabis.

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1. Introduction

It is estimated that in 2009, between 125 and 203 million people of the world population aged 15–64 (corresponding to between 2.8% and 4.5%) had consumed cannabis at least once in the past year [1]. Herbal cannabis contains more than 60 cannabinoids, which are only found in the plant genus Cannabis. Δ^9 -Tetrahydrocannabinol (THC) is considered to be the most potent psychoactive agent [2]. Cannabinoid-related psychological and physiological effects are well reported [3–8]. The acute toxicity of cannabinoids is said to be low [3] and there is little public awareness of the potentially hazardous cardiovascular effects associated with the consumption of cannabis. Compared to high-nicotine cigarettes, cannabis is considered to induce significantly higher heart rates, cardiac output, blood pressure, and venous carboxy-hemoglobin levels, which significantly reduces exercise time until the onset of anginal symptoms [9]. Several, assumably cannabinoid-triggered arrhythmias and myocardial infarctions have been described [10–18]. However, none of these cases mentions blood levels of THC at the time of occurrence of the cardiovascular event. Fatal cannabis intoxications have been described as well [19,20]; full post-mortem histopathological examinations were not carried out though. Post-mortem toxicological analyses revealed THC-levels in whole blood between 2 and 22 $\mu\text{g/l}$ [20]. A young soldier who had vainly tried to commit

suicide by smoking cannabis spent 4 days in coma and claimed afterwards that others had used this method effectively before [21]. Naturally, diagnoses of death due to cannabis intoxication without autopsy, full histopathological examinations, serum markers of myocardial necrosis and genetic analyses is not assured according to actual standards [22–24] and must leave questions unanswered.

We describe the cases of two young men who died unexpectedly under the acute influence of cannabinoids. To our knowledge, these are the first cases of fatal cannabis smoking where full postmortem investigations were carried out.

2. Case reports

Postmortem investigations (autopsy, toxicological, histological and immunohistochemical examinations) were performed according to medicolegal standards [22–24]. For the toxicological analyses, a general unknown screening was performed using the immunoassays, GC/MS and HPLC-DAD. THC and its metabolites were determined by GC/MS using deuterated standards. This method was fully validated. Immunohistochemical reactions were performed with the antibody C5b-9 (monoclonal mouse anti-human, Abcam Inc., Cambridge, USA). A targeted mutational analysis of the major concerned ion-channel genes SCN5A (NC_008934), KCNH2 (NC_008916), KCNQ1 (NG_008935), and of the cardiac ryanodine receptor gene RyR2 (NG_008799) including 29 exons (3, 8, 10, 12, 14, 15, 37, 41, 44–47, 49, 50, 83, 88–90, 93–96, 97, 99–103, 105) was performed using polymerase chain reaction (PCR) with published [25,26] and redesigned primers (primer sequences

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59 upon request). Genes with a rare frequency are not completely
60 screened so far. Direct sequencing of the amplicons was performed
61 as described previously [25].

62 3. Case 1

63 A 23-year-old male without known relevant illnesses suddenly
64 collapsed while using public transport and died after 40 min of
65 unsuccessful cardiopulmonary resuscitation with a clinical picture
66 of ventricular fibrillation. A small amount of marijuana was found
67 in his pockets.

68 *Autopsy* revealed a young man of slim build (BMI 21.3, 77.7 kg,
69 >0.6 of the body weight). Macromorphological findings did not
70 identify the cause of death. The interior organs were highly
71 congested with blood. Beginning arteriosclerotic changes of the
72 abdominal aorta and all three major coronary vessels were seen as
73 well as a remarkable hypertrophy of the cardiac muscle (480 g).
74 There was no significant thickening of the heart ventricles (right
75 chamber: 3 mm, left chamber: 13 mm). The lungs exhibited edema
76 (right lung, 0.74 kg/left lung, 0.72 kg).

77 *Histopathological examinations* showed different signs of a
78 cardiac hypertrophy and a thrombus formation in a small cardiac
79 vessel (Fig. 1). Immunohistochemical reaction of the cardiac
80 muscle with C5b-9 antibody showed negative results. There were
81 no signs of an infectious disease, however signs of hypertrophy
82 (enlarged myocyte nuclei, interstitial fibrosis) could be revealed.
83 Both lungs showed protein-rich edema with several iron-negative
84 macrophages, severe blood-congestion with microscopic bleedings
85 and a cholesterol granuloma (Fig. 2).

86 *Toxicological examinations* proved the acute influence of
87 cannabis (femoral blood: THC 5.2 ng/ml, 11-OH-THC 1.8 ng/ml,
88 THC-COOH 12.9 ng/ml; brain tissue: THC 13.4 ng/g, 11-OH-THC
89 7.0 ng/g, THC-COOH 4.3 ng/g). Screening tests for other common
90 drugs showed negative results.

91 *Postmortem genetic analysis* of the most common genes,
92 associated with potentially lethal channelopathies [27], such as long
93 QT syndromes (LQTS; genes KCNQ1, KCNH2, SCN5A), the Brugada
94 syndrome (BrS; gene SCN5A), or catecholaminergic polymorphic
95 ventricular tachycardia (CPVT; gene RyR2) detected polymorphisms
96 in relevant genes (KCNQ1, KCNH2, SCN5A, RyR2). These polymor-
97 phisms do not change the amino-acid formation of the genes.

98 As there is no known medical history and as both cardiac
99 chambers showed normal thicknesses, we assume a dilatative
100 cardiomyopathy as explanation for the hypertrophy of the cardiac
101 muscle. We concluded that death occurred most possibly due to

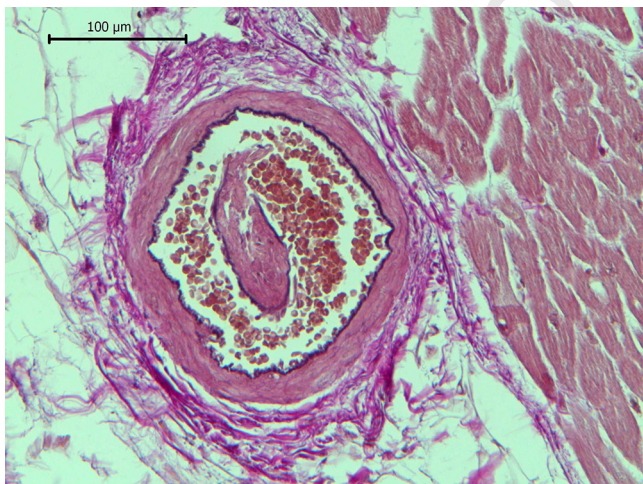


Fig. 1. Part of a thrombus within a small artery located within the epicardial fat tissue (Elastica van Gieson staining, bar = 100 µm).

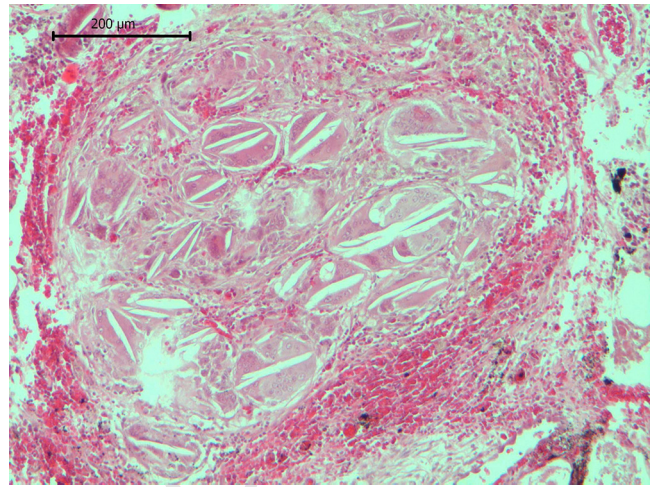


Fig. 2. Granulomatous inflammation with acicular cholesterol-like spaces surrounded by multinucleated giant cells (H&E staining, bar = 200 µm).

cardiac arrhythmia with cardiac hypertrophy and consecutive
stasis-associated thrombus formation of a small cardiac vessel
under the acute influence of cannabis.

105 4. Case 2

106 A 28-year-old male with a history of substance abuse (alcohol,
107 amphetamines and cocaine until about 2 years before death;
108 occasionally cannabis), but without known cardiovascular diseases
109 was found dead at home by his girlfriend. Next to the body an
110 ashtray, rolling paper and a sealable plastic bag containing
111 remnants of marijuana were found.

112 The *autopsy* showed a young man of athletic build (BMI 25.5,
113 91 kg). No macromorphologically visible cause of death could be
114 found. The interior organs were highly congested with remarkably
115 fluid blood. Neither the cardiac muscle (430 g; <0.5 of the body
116 weight) nor the great and coronary artery vessels revealed
117 pathological findings. Both lungs exhibited edema (right lung,
118 0.88 kg/left lung, 0.77 kg). The urinary bladder contained 400 ml of
119 urine.

120 *Histopathological examinations* of the heart showed several foci
121 of single cell necrosis (Fig. 3) and a negative immunohistochemical
122 reaction with C5b-9 antibody. There were no signs of an infectious
123 disease. Furthermore, protein-rich edema of the lungs with severe

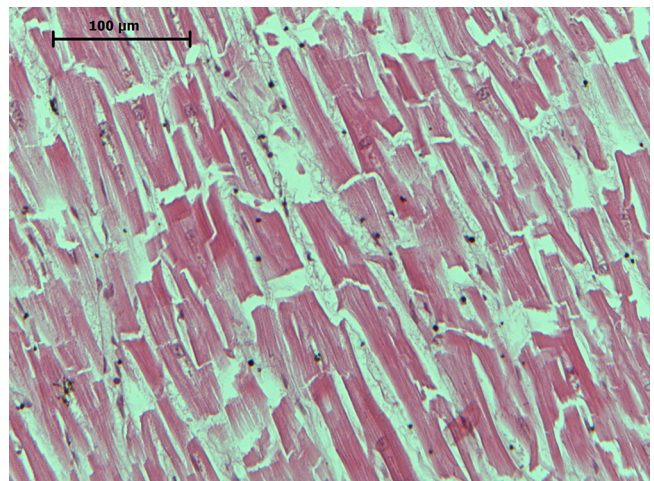


Fig. 3. Focus of single cell necrosis (H&E staining, bar = 200 µm).

blood-congestion, microscopic bleedings and several iron-negative macrophages similar to Section 3 were seen.

Toxicological examinations proved the acute influence of cannabis (femoral blood: THC 1.9 ng/ml, 11-OH-THC 0.8 ng/ml, THC-COOH 10.1 ng/ml; brain tissue: THC 6.3 ng/g, 11-OH-THC 2.3 ng/g, THC-COOH 2.3 ng/g). General unknown screening for other common drugs was negative with the exception of nicotine and caffeine levels.

Chemical examinations showed an elevation of myoglobin (femoral blood: 5050 ng/ml, reference range < 90 ng/ml) and gave a normal result for troponin T (femoral blood: 13 ng/l, reference range < 14 ng/l).

Postmortem genetic analysis of the most common genes, associated with potentially lethal channelopathies [27], such as LQTS (genes KCNQ1, KCNH2, SCN5A), BrS (gene SCN5A), or CPVT (gene RyR2) detected polymorphisms in relevant genes (KCNQ1, KCNH2, SCN5A, RyR2). However, these polymorphisms do not change the amino-acid formation of the genes.

We concluded that death occurred due to acute global cardiac failure under the acute influence of cannabis.

5. Discussion

After exclusion of other causes of death we assume that the young men died from cardiovascular complications evoked by smoking cannabis. In Section 3 signs of an underlying dilatative cardiomyopathy were found which makes a sudden cardiac death highly probable [24]. In Section 4 no distinct underlying cardiovascular diseases could be revealed which leaves space for interpretation; the elevation of myoglobin could be explained by long-lasting resuscitation efforts. Both men showed protein-rich pulmonary edema and severe blood-congestion with microscopic bleedings. Numerous iron-negative macrophages were found. Microscopic bleedings in the lung tissue might be the result of drug-induced hypoxia [28]. Alveolar macrophage exudation is considered to be a major pulmonary effect of smoking cannabis [29]; cholesterol granulomas (as seen in Section 3, Fig. 2) surrounded by multinucleated giant cells could also be found in rats exposed to marijuana smoke [30].

The assumption of fatal heart failure in both cases is corroborated by the acute effects of marijuana, including a marked increase in heart rate that may result in cardiac ischemia in susceptible individuals, lesser increases in cardiac output, supine blood pressure and postural hypotension [9,15]. We assume the deaths of these two young men occurred due to arrhythmias evoked by smoking cannabis; however this assumption does not rule out the presence of predisposing cardiovascular factors.

The thrombus formation in a small cardiac vessel would (Section 3) fits to other described vascular complications of marijuana like venous thrombosis or Raynaud's phenomenon [8]. This could fit with the finding that cannabis induces ischemic ST-segment depression due to increased myocardial oxygen demand and decreased myocardial oxygen delivery at the onset of exercise-induced angina pectoris [6].

One could also consider a significant but subclinical arterial hypertonia that might have been worsened by smoking cannabis [9], potentially leading to a hypertensive crisis. However both cases do not show specific macromorphological signs and direction-giving medical findings (e.g. from general practitioners) do not exist.

The absolute risk of cannabis-related cardiovascular effects can be considered to be low, as the baseline risk for most cannabis smokers is low and cannabis-induced changes are transient [8,18]. The risk of myocardial infarction is elevated almost 5-fold in the hour after smoking cannabis and declines rapidly afterwards [14]. Consequently, the relative risk for cardiovascular effects is most

probably increased within this period. Persons who are at high risk for cardiovascular diseases are even recommended to avoid the use of cannabis [15]. The intravenous LD₅₀ for THC in rats is considered to be 28.6 mg (27.4–29.85 mg) per kilogram [31], corresponding to an estimated intravenous lethal dose in humans of around 2000 mg in total or 30 mg per kilogram [3]. Nevertheless, it is impossible to predict how certain individuals respond to cannabis smoke, as underlying illnesses and complicating factors [20] may be unknown.

The presented cases highlight the potentially hazardous cardiovascular effects of cannabis in putative healthy young persons.

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