



## Acute Hippocampal Encephalopathy in Heavy Cannabis Users: About 2 Cases

Quang Tuan Rémy Nguyen, Alban Gravier, Constance Lesoil, Alexandre Bedet, Camille Petit-Hoang, Matthieu Mahevas, Armand Mekontso-Dessap, Jérôme Hodel, Anne-Catherine Bachoud-Lévi, Laurent Cleret de Langavant

### ► To cite this version:

Quang Tuan Rémy Nguyen, Alban Gravier, Constance Lesoil, Alexandre Bedet, Camille Petit-Hoang, et al.. Acute Hippocampal Encephalopathy in Heavy Cannabis Users: About 2 Cases. The American Journal of Medicine, 2020, 133, pp.e360 - e364. 10.1016/j.amjmed.2019.11.018 . hal-03490133

**HAL Id: hal-03490133**

**<https://hal.science/hal-03490133>**

Submitted on 1 Jul 2022

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1 **Acute hippocampal encephalopathy in heavy cannabis users: about two cases**

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3 **Authors**

4 Quang Tuan Rémy NGUYEN, MD<sup>1,2,3,4</sup>, Alban GRAVIER, MD<sup>1</sup>, Constance LESOIL, MD<sup>1</sup>,  
5 Alexandre BEDET, MD<sup>5</sup>, Camille PETIT-HOANG, MD<sup>6</sup>, Matthieu MAHEVAS, MD<sup>7</sup>,  
6 Armand MEKONTSO-DESSAP, MD, PhD<sup>4,5</sup>, Jérôme HODEL, MD, PhD<sup>4,8</sup>, Anne-Catherine  
7 BACHOUD LEVI, MD, PhD<sup>1,2,3,4\*</sup>, Laurent CLERET DE LANGAVANT, MD, PhD<sup>1,2,3,4,9\*</sup>

8

9 **Affiliations**

10 1 Assistance Publique-Hôpitaux de Paris, CHU Henri Mondor, service de Neurologie, Créteil,  
11 F-94010 France

12 2 INSERM U955 Equipe E01, Institut Mondor de recherche biomédicale, Neuropsychologie  
13 Interventionnelle, Créteil, France

14 3 Département d'Etudes Cognitives, Ecole Normale Supérieure, PSL University, Paris,  
15 France

16 4 Université Paris Est, Faculté de Médecine, 94000 Créteil, France

17 5 Assistance Publique-Hôpitaux de Paris, CHU Henri Mondor, service de Médecine Intensive  
18 Réanimation, Créteil, F-94010 France

19 6 Assistance Publique-Hôpitaux de Paris, CHU Henri Mondor, service de Néphrologie,  
20 Créteil, F-94010 France

21 7 Assistance Publique-Hôpitaux de Paris, CHU Henri Mondor, service de Médecine interne,  
22 Créteil, F-94010 France

1 8 Assistance Publique-Hôpitaux de Paris, CHU Henri Mondor, service de Neuroradiologie,  
2 Créteil, F-94010 France

3 9 Global Brain Health Institute, UCSF, San Francisco, USA

4 \*both authors contributed equally to the study.

5

6 **Corresponding author**

7 Dr Laurent Cleret de Langavant

8 Service de Neurologie

9 CHU Henri Mondor

10 Créteil, F-94010 France

11 Phone +33 1 49 81 23 08

12 Fax + 33 1 49 81 23 26

13 laurent.cleret@gbhi.org

14

15 **Funding source**

16 LCL and ACBL are supported by ANR-17-EURE-0017.

17

18 **Conflicts of Interest**

19 The authors report no conflict of interest.

20

1    **Author Contributions**

2    Conception and design of the study: QTRN, AG, ACBL, LCL. Acquisition and analysis of  
3    clinical data: QTRN, AG, CL, AB, CPH, MM, AMD, JH, ACBL, LCL. Drafting the  
4    manuscript: QTRN, AG, ACBL, LCL. Critical review of the manuscript: QTRN, AG, CL,  
5    AB, CPH, MM, AMD, JH, ACBL, LCL. Preparation of figure: JH.

6

7    **Keywords**

8    Cannabis, Memory, Encephalopathy, Hippocampus, Addiction

9

10   **Running head**

11   Cannabis-related hippocampal encephalopathy

12

1   **Abstract:**

2   Background:

3   Cannabis use is increasing worldwide despite the various health effects of this substance.

4   Methods:

5   We report two cases of acute hippocampal encephalopathy in heavy cannabis users (>10  
6   joints/day).

7   Results:

8   In both male patients, acute encephalitis was suspected. Brain MRI diffusion-weighted  
9   sequences showed bilateral high signal abnormalities in hippocampal regions. Patients had  
10   renal dysfunction, rhabdomyolysis and inflammatory syndrome. Investigations showed no  
11   evidence of infectious or autoimmune encephalitides. Repeated electroencephalograms  
12   revealed no epileptic activity. Clinical, biological and MRI acute abnormalities improved  
13   within weeks. New exposition to cannabis yielded a new episode of encephalopathy. In both  
14   patients, severe long-lasting episodic memory impairment associated with hippocampal  
15   atrophy were observed several months later.

16   Conclusions:

17   Health professionals should be aware of this cannabis-related syndrome given its severe and  
18   long-lasting effects.

19

## 1    **Introduction:**

2    The number of cannabis users is increasing along with the progressive legalisation of both  
3    recreational and medical cannabis worldwide. Acute cardiovascular, respiratory, cognitive,  
4    psychiatric and public health consequences have been reported in cannabis users, as well as  
5    chronic cardiovascular and respiratory effects.<sup>1,2</sup> The cannabinoid hyperemesis syndrome<sup>3</sup>  
6    associates cyclical nausea, vomiting and abdominal pain relieved by hot showers.

7    Here, we report two cases of acute hippocampal encephalopathy in heavy cannabis users, with  
8    long-lasting memory impairment and delayed hippocampal atrophy.

## 9    **Case 1**

10    In October 2016, a 32-year-old man was admitted for delirium associated with inflammatory  
11    syndrome, rhabdomyolysis, and acute kidney injury.

12    He was a heavy user of cannabis (10 joints/day since his twenties), tobacco and alcohol (30-  
13    45 units/week). He had generalized epilepsy diagnosed nine years earlier and treated with  
14    Levetiracetam 1000 mg/day and Lamotrigine 200 mg/day. He had not travelled abroad in the  
15    preceding year.

16    The patient was found at home, disoriented and calm. The first clinical examination revealed  
17    delirium and agitation. The first blood tests found elevated leukocytes ( $30000/\text{mm}^3$ , 90%  
18    neutrophils), subnormal creatinine ( $117\text{ }\mu\text{mol/L}$ ) and normal creatine kinase ( $\text{CK} = 250\text{ IU/L}$ ).  
19    Within 12 hours, the patient's clinical condition worsened with severe delirium, agitation, and  
20    fever ( $38.5^\circ\text{C}$ ). A second blood test demonstrated rhabdomyolysis ( $\text{CK} = 1600\text{ IU/L}$ ), renal  
21    dysfunction (serum creatinine  $558\text{ }\mu\text{mol/L}$  at day 3) and inflammatory syndrome ( $33.900$   
22    leukocytes/ $\text{mm}^3$ , C-Reactive Protein  $\text{CRP} = 61.5\text{ mg/L}$ , procalcitonin  $= 2.96\text{ }\mu\text{g/L}$ ). Troponin  
23    T ( $20\text{ ng/L}$ ) and NT-proBNP ( $8579\text{ IU}$ ) raised with no electrocardiogram changes. Serum

lactate and carboxyhemoglobin were normal. The patient was admitted in intensive care unit for suspicion of acute encephalitis.

The cerebrospinal fluid analysis found no evidence of meningitis ( $<10$  leukocytes /mm<sup>3</sup>, no germs, normal protein and glucose levels). Further investigations showed no evidence of antibodies related to autoimmune encephalitides. The toxicological test was positive for cannabis but negative for other drugs and alcohol. The brain MRI achieved 2 days later showed bilateral hippocampal abnormalities (Figure 1) with no gadolinium enhancement. The repeated electroencephalograms (EEG) showed no epileptic activity.

The patient was treated by intravenous acyclovir despite two negative Herpes Simplex Virus Polymerase Chain Reaction (PCR) in the cerebro-spinal fluid. Delirium and agitation improved after one week, but episodic memory impairment remained severe (Table 1).

Biological abnormalities were normalized within five days. One month later, the patient returned home and discontinued his alcohol and cannabis intoxications. In May 2017, memory performance remained severely impaired despite slight improvement (Table 1).

In June 2017, the patient was admitted for delirium, rhabdomyolysis (CK = 12984 IU/L), acute kidney injury (creatinine = 1158  $\mu$ mol/L), and hippocampal abnormalities on brain MRI. The evolution was similar to the first episode, without any treatment with acyclovir. Investigations revealed heavy and recent consumption of cannabis.

Brain MRI revealed hippocampal atrophy in September 2017 (Figure 1). Memory performance remained impaired in July 2018, despite discontinuation of cannabis and alcohol intoxications. The patient resumed work under supervision.

## Case 2

In July 2018, a 38-year-old man was admitted for delirium, fever, rhabdomyolysis and renal dysfunction.

1 He was a heavy user of cannabis (10 to 15 joints/day for 10 years) but not of tobacco or  
2 alcohol. He had a seizure associated with transient cognitive disorders, renal dysfunction and  
3 rhabdomyolysis in October 2016 and had been treated since with Sodium Valproate 1500  
4 mg/day. He had not travelled abroad in the preceding year.

5 In July 2018, the patient was found at home sitting on the toilet and stained with stool and  
6 urine. The clinical examination confirmed a delirium without fever. Blood tests revealed  
7 severe rhabdomyolysis (CK = 64815 IU/L), renal dysfunction (creatinine 124  $\mu$ mol/L) and  
8 inflammatory syndrome (neutrocytes 37.000/mm<sup>3</sup>, but CRP=3.1mg/L). Serum lactate and  
9 carboxyhemoglobin were normal. Within hours, a fever (38.2°C) appeared and the patient's  
10 consciousness deteriorated. He was intubated and hospitalized in intensive care unit for  
11 suspicion of acute encephalitis.

12 Cerebro-spinal fluid analysis found no evidence of meningitis (<10 leukocytes, no germs,  
13 normal glucose level but elevated protein 0.7 g/L). Blood and cerebro-spinal fluid tests  
14 showed neither evidence of antibodies suggestive of autoimmune encephalitides.

15 Toxicological testing was positive for cannabis and negative for synthetic cannabinoid or  
16 other drugs. The repeated EEG did not reveal any epileptic activity. Despite raised troponin T  
17 (297 ng/L), there was no sign of acute coronary syndrome on electrocardiogram or  
18 echocardiography. The brain MRI on day 2 after admission showed bilateral hippocampal  
19 abnormalities, with no gadolinium enhancement (Figure 1).

20 The patient was treated with intravenous acyclovir which was halted after two negative  
21 Herpes Simplex Virus PCR in the cerebro-spinal fluid. Under the suspicion of autoimmune  
22 limbic encephalitis, the patient received intravenous immunoglobulins (2g/kg). Consciousness  
23 improved allowing extubation (day 2) and biological disorders normalized within a week.



Episodic memory disorders remained severe (Table 1). Thirteen days after admission, brain MRI found persistent hippocampal abnormalities. Eight months later, episodic memory remained severely impaired with a significant impact in daily life and incapacity to return to work (Table 1). At that time, the brain MRI revealed hippocampal atrophy (Figure 1).

## **Discussion:**

We reported two cases of acute hippocampal encephalopathy in heavy cannabis users. Both patients had a history of epilepsy. The biological abnormalities included renal dysfunction, rhabdomyolysis, and inflammatory syndrome. The clinical, biological and brain MRI abnormalities improved within days to weeks with the exception of long-lasting episodic memory impairment and hippocampal atrophy. Both patients had two episodes following heavy consumption of natural cannabis.

We found no evidence of conditions known to cause hippocampal lesions: ischemic stroke, transient global amnesia, status epilepticus, herpetic encephalitis, autoimmune limbic encephalitis, anoxic, hypoglycemic or carbon monoxide encephalopathy were discarded.<sup>4</sup> Rather, these abnormalities could correspond to the effects of two psychoactive components of cannabis,  $\Delta$ -9-tetrahydrocannabinol ( $\Delta$ -9-THC) and cannabidiol (CBD), that have distinct affinity for cannabinoid type 1 (CB1R) and type 2 receptors (CB2R). The CB1R are found in neuron terminals of several brain regions including the hippocampus<sup>5</sup> as well as in enteric nervous system, striated myocardial and skeletal muscles<sup>6</sup> and kidneys.<sup>7</sup> The cannabinoid type 2 receptors (CB2R) are found in immune cells.<sup>8</sup>

Although CBD is described as anticonvulsant,<sup>9</sup>  $\Delta$ -9-THC might be proconvulsant.<sup>10</sup> In both cases here, cannabis consumption preceded epilepsy occurrence suggesting a causal role of cannabis. Acute kidney injuries were reported in cannabis users and explained by acute

tubular necrosis secondary to dehydration in hyperemesis syndrome or to rhabdomyolysis, or hypothetically caused by direct toxicity of synthetic cannabinoid.<sup>11</sup> Noteworthy, our patients used natural cannabis and did not exhibit hyperemesis syndrome. The spontaneous improvement of their renal function suggested acute tubular necrosis. Rhabdomyolysis was reported after synthetic cannabis consumption.<sup>12</sup> Cannabis might interfere with CB1R in striated muscle mitochondria impacting oxidative activity and glucose metabolism.<sup>6</sup>

A long-lasting episodic memory disorder followed the acute hippocampal encephalopathy episodes in both patients. The tropism of cannabis neurotoxicity for hippocampus may be explained by hippocampal high concentration of CB1R. Long term memory deficits are reported in chronic cannabis users.<sup>13</sup> Reduced hippocampal grey matter volume is associated to cannabis use.<sup>14</sup> These long-lasting effects may be caused by  $\Delta$ -9-THC<sup>15</sup> while CBD may be neuroprotective.<sup>16</sup>

Acute hippocampal encephalopathy can occur in heavy cannabis users, but both reported cases could have genetic predisposition to this syndrome.<sup>17</sup> Furthermore, cannabis withdrawal after admission might have worsened patients' condition. Depriving the CB1R might cause a cascade of cerebral, renal, muscular, and cardiac disorders, while the CB2R liberation might cause an inflammatory syndrome. Future work is needed to ascertain the role of cannabis components and to assess the therapeutic value of using CBD in this syndrome.

## Acknowledgements

The authors thank both patients who agreed for reporting their history.

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## Figure legend

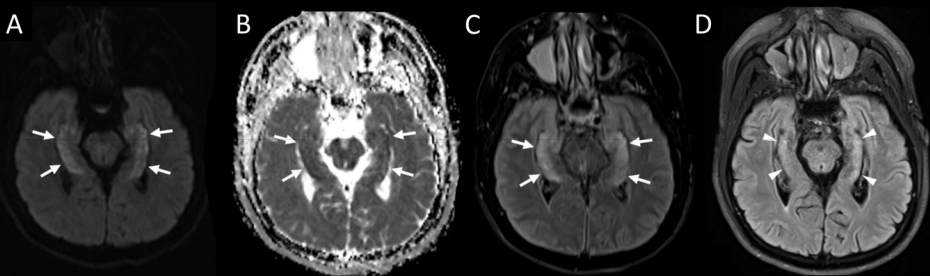
### Figure 1. Hippocampal abnormalities on brain MRI

Signal intensity changes on brain MRI in case 1 (A, B, C, D) and case 2 (E, F, G, H). In both patients, during the acute phase, an area of signal abnormality is observed in both hippocampal regions in Diffusion-Weighted (A, E), Apparent Diffusion Coefficient (B, F) and Fluid Attenuated Inversion Recovery sequences (C, G). (D) and (H) illustrate hippocampal atrophy on Fluid Attenuated Inversion Recovery sequence during the chronic phase.

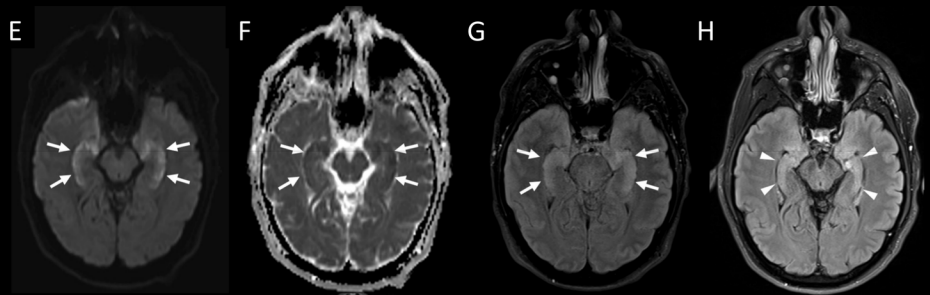
## Table legend

**Table 1. Cognitive performance at acute and chronic phases.** Episodic memory is severely impaired in both patients, at both acute and chronic phases. The patient case 2 additionally shows naming deficits partly explained by lower proficiency in French language. \*\*\* means that patients perform below 3 standard deviations from the mean score of a group of controls of the same age and educational level. FCSRT: Free and Cued Selective Reminding Test (Buschke, 1984). ROCF: Rey-Osterrieth Complex Figure (Osterrieth, 1944). Trail Making Test (Reitan, 1955). Stroop test (Stroop, 1935). Language naming (Deloche, 1996). Pyramids and Palm Trees test (Howards and Patterson, 1992). Mini Mental Status (Folstein, 1975).

## Case 1



## Case 2



**Table 1**

	Case 1		Case 2	
Cognitive Assessment Date	Nov 2016	May 2017	Aug 2018	Feb 2019
Episodic Memory				
FCSR Identification /16	16	16	16	16
FCSRT Immediate Cued Recall /16	12***	11***	8***	9***
FCSRT Total Free Recall /48	3***	14***	7***	11***
FCSRT Total Recall 1 /16	4***	8***	4***	6***
FCSRT Total Recall 2 /16	0***	13***	6***	7***
FCSRT Total Recall 3 /16	0***	11***	8***	12***
FCSRT Delayed Free Recall /16	0***	6***	0***	0***
FCSRT Delayed Total Recall /16	0***	14***	6***	5***
ROCF Recall	0***	0***	3***	9***
Attention and Executive Function				
Forward Digit Span	6	6	6	6
Backward Digit Span	4	4	4	5
Trail Making Test A (sec)	24	27	37	42
Trail Making Test B (sec)	47	53	87	102
Stroop Colors	57	52	55	56
Stroop Words	47	44	42	46
Stroop Interference	90	93	107	99
Categorical fluency (animals 120 sec)	27	26	23	17
Lexical fluency (letter P 120 sec)	21	18	8	10
Instrumental Function				
Language naming /80	79	80	60***	69***
Pyramid and Palm Tree Test /52	49	50	-	-
Calculation /28	28	28	28	28
Gestures (ideomotor, motor) /40	40	40	40	40
ROCF Copy	36 (type I)	36 (type I)	36 (type IV)	36 (type I)
Global efficiency				
Mini Mental Status Examination /30	24	26	22	23