Cannabis and Stroke
Systematic Appraisal of Case Reports

Daniel G. Hackam, MD, PhD, FRCPC

Background and Purpose—An increasing number of case reports link cannabis consumption to cerebrovascular events. Yet these case reports have not been scrutinized using criteria for causal inference.

Methods—All case reports on cannabis and cerebrovascular events were retrieved. Four causality criteria were addressed: temporality, adequacy of stroke work-up, effects of rechallenge, and concomitant risk factors that could account for the cerebrovascular event.

Results—There were 34 case reports on 64 patients. Most cases (81%) exhibited a temporal relationship between cannabis exposure and the index event. In 70%, the evaluation was sufficiently comprehensive to exclude other sources for stroke. About a quarter (22%) of patients had another stroke after subsequent re-exposure to cannabis. Finally, half of patients (50%) had concomitant stroke risk factors, most commonly tobacco (34%) and alcohol (11%) consumption.

Conclusions—Many case reports support a causal link between cannabis and cerebrovascular events. This accords well with epidemiological and mechanistic research on the cerebrovascular effects of cannabis. **(*Stroke*. 2015;46:852-856. DOI: 10.1161/STROKEAHA.115.008680.)**

Key Words: case management ■ epidemiology ■ risk factors ■ stroke ■ substance-related disorders

Cannabis sativa is the most popular illicit drug consumed in Western societies. This is, in part, because of an assumption among users that cannabis is a safe recreational drug. Conversely, several experts think that cannabis is a risk factor for stroke and its use should be minimized.[1] This perspective is largely premised on case reports linking cannabis exposure to stroke.

One concern is that these case reports have not been formally rated using causality criteria. In particular, the following questions have not been synthesized across the case reports: (1) Was there a temporal relationship between cannabis exposure and the stroke or transient ischemic attack? (2) Were other potential stroke causes excluded through a detailed stroke work-up? (3) Were additional risk factors present that could have explained the stroke (eg, coingested illicit substances)? (4) Was rechallenge with cannabis associated with recurrent stroke? These criteria are based on the Naranjo probability scale for inferring drug-associated causality for adverse events.[2]

Methods

This systematic review adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses. The search combined keywords for cannabis and cerebrovascular disease and was executed in Medline and EMBASE from inception until November 30, 2014 (see Appendix in the online-only Data Supplement for the detailed search strategy). Conference abstracts were permitted. To be included, cases had to undergo parenchymal imaging.

A temporal relationship was defined as a stroke or transient ischemic attack ensuing within 24 hours of consumption of cannabis. A detailed stroke work-up entailed computed tomographic angiography, magnetic resonance angiography, or catheter angiography with parenchymal imaging; blood testing for thrombophilia and vasculitis; and cardiac work-up involving prolonged electrocardiographic monitoring and transthoracic or transesophageal echocardiography. All information for this review was collected from the published case reports themselves.

Results

A total of 989 citations were identified; after relevance screening, the full text of 56 articles were retrieved (Figure). Of these, 34 published case reports or case series were eligible, representing a total of 64 patients (Table; Table I in the online-only Data Supplement).[3–36] Most cases were men (80%); the median age was 32 (range 15–64) years. The majority of infarctions occurred in the anterior circulation (56%); 3 cases involved both anterior and posterior circulations (5%); and the remainder either occurred in the posterior circulation (36%) or were not classified (3%).

Most cases (81%) exhibited a temporal relationship between cannabis exposure and the index cardiovascular event. In 70% of cases, the evaluation was sufficiently comprehensive to exclude other sources of stroke. About a quarter of patients (22%) had recurrent stroke from subsequent re-exposure to

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From the Division of Clinical Pharmacology, Department of Medicine, Western University, London, Ontario, Canada.
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Correspondence to Daniel G. Hackam, MD, PhD, FRCPC, 1400 Western Rd, London, Ontario, Canada N6G 2V2. E-mail dhackam@uwo.ca

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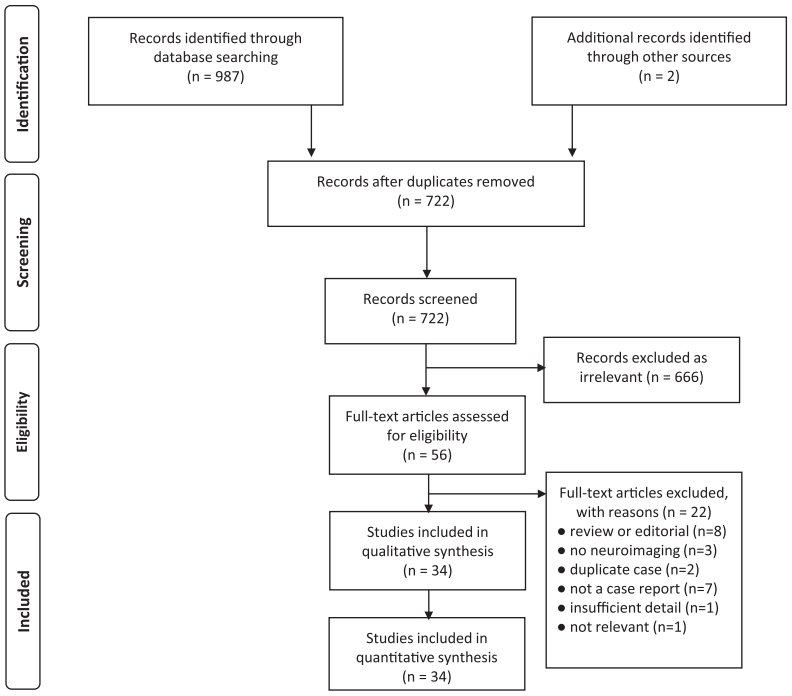

Figure. Literature search and selection.

cannabis. Half of patients (50%) had concomitant risk factors for stroke, most commonly tobacco (34%) and alcohol (11%). Three quarters of patients (48 of 64) underwent toxicological analysis for common street drugs; results were positive for drugs other than cannabis in only 2 cases (Table II in the online-only Data Supplement).

Table. Case Reports With Causality Appraisal

Report	Year Published	Age, y/Sex	Territory of Infarct	Temporality	Other Causes of Stroke Excluded	Concomitant Stroke Risk Factors	Subsequent Re-exposure and Effect
Alvaro et al[3]	2002	33/M	Right PCA	Yes	Yes	Acute coital cephalgia	…
Baharnoori et al[4]	2014	22/M	Right lentiform nucleus and corona radiata	Yes	Yes	None	…
Bal et al[5]	2009	22/M	Bilateral cerebellum and left temporal lobe	Yes	Yes	None	…
Barnes et al[6]	1992	30/M	Left cerebellar hemisphere; left striatocapsular area	Yes	Yes	Tobacco	Stroke
Drumm et al (1)[7]	2012	34/F	Multiple arterial territories	Yes	Yes	Unclear	Stroke
Drumm et al (2)[7]	2012	29/F	Multiple arterial territories	Yes	Yes	Unclear	Stroke
Drumm et al (3)[7]	2012	64/M	Right MCA	Yes	Yes	Unclear	Stroke
El Scheich et al[8]	2013	16/M	Adjacent to the internal capsule at the lateral portion of the left thalamus	Yes	No	Anabolic steroid	…
Finsterer et al[9]	2004	37/M	Right occipital subcortex	Yes	Yes	Tobacco, mild dyslipidemia	…
Giray et al[10]	2011	35/M	Left MCA	No	No	None	…
Haubrich et al[11]	2005	50/M	Left parietal subcortex	Yes	Yes	Hypertension, tobacco	…
Ibrir et al[12]	2014	34/M	Left sylvian fissure	No	Yes	Tobacco, alcohol	…
Inal et al[13]	2014	23/M	Left temporal lobe	No	Yes	Tobacco, alcohol	…
Lawson and Rees[14]	1996	22/M	Right posterior external capsule, upper part of the internal capsule and corona radiata	Yes	No	Tobacco, alcohol, LSD	…
Maguire et al[15]	2011	40/M	Left dorsolateral frontal cortex	No	No	Amphetamine, alcohol, diazepam, tobacco	…

(*Continued*)

Table. Continued

Report	Year Published	Age, y/Sex	Territory of Infarct	Temporality	Other Causes of Stroke Excluded	Concomitant Stroke Risk Factors	Subsequent Re-exposure and Effect
Marinella[16]	2001	18/M	Right occipital lobe	Yes	No	Factor V Leiden	…
Mateo et al[17]	2005	36/M	Left temporal and right parietal, left/right frontal, right posterior-temporal and lower parietal	Yes	Yes	Alcohol	Stroke x 2
McCarron and Thomas[18]	1997	29/M	Right MCA	No	No	Tobacco, alcohol	…
Mesec et al[19]	2001	23/M	Left cerebral hemisphere	Yes	No	Tobacco, alcohol	…
Mouzak et al (1)[20]	2000	18/M	Leukoariosis	Yes	Yes	Tobacco	…
Mouzak et al (2)[20]	2000	26/M	Leukoariosis	Yes	Yes	Tobacco	…
Mouzak et al(3)[20]	2000	30/M	Leukoariosis	Yes	Yes	None	…
Nouh et al[21]	2014	32/F	Bilateral occipital infarcts	Yes	Yes	Migraines	…
Oyinloye et al[22]	2014	26/M	Left corpus striatum and insula cortex	Yes	Yes	None	…
Pazderska et al[23]	2009	35/F	Multiple arterial territories (especially right frontal lobe)	No	No	Tobacco, cocaine	Stroke x 2
Reece[24]	2009	56/M	Parieto-occipital cortex	No	No	Mild hypertension, tobacco	…
Renard and Gaillard[25]	2008	34/F	Right temporal lobe hemorrhage	Yes	Yes	Tobacco, buprenorphine	…
Renard et al[26]	2012	33/M	Right MCA and bilateral ACA-MCA watershed zones	No	Yes	Tobacco	…
Russmann et al[27]	2002	27/M	Left MCA	Yes	No	Chemotherapy, tobacco	…
Santos et al[28]	2014	27/M	Left basal ganglia; right lenticulostriate area; right frontal and parietal (ACA and MCA)	No	Yes	None	Stroke x 2
Singh (1)[29]	2012	15/M	Right cerebellum	Yes	Yes	None specified	…
Singh et al (2)[29]	2012	16/M	Bilateral cerebellum	No	Yes	None specified	…
Singh et al (3)[29]	2012	17/M	Left cerebellum	Yes	Yes	None specified	…
Singh et al (4)[29]	2012	22/M	Right cerebellum	Yes	Yes	None specified	Stroke
Singh et al (5)[29]	2012	27/F	Left MCA branch	Yes	Yes	Tobacco	…
Singh et al (6)[29]	2012	28/F	Right cerebellum	Yes	Yes	None specified	…
Singh et al (7)[29]	2012	37/M	Left MCA branch	Yes	Yes	None specified	…
Singh et al (8)[29]	2012	44/M	Bilateral cerebellum	Yes	No	None specified	Stroke
Singh et al (9)[29]	2012	44/F	Left MCA branch	Yes	No	None specified	…
Singh et al (10)[29]	2012	49/M	Right MCA branch	Yes	Yes	None specified	…
Singh et al (11)[29]	2012	52/F	Right MCA/ACA	Yes	No	Hypertension, tobacco	…
Singh et al (12)[29]	2012	50/M	Bilateral cerebellum	Yes	Yes	Hypertension	Stroke
Singh et al (13)[29]	2012	56/M	Right PCA and cerebellum	Yes	No	PFO	Stroke
Singh et al (14)[29]	2012	58/M	Left MCA branch	Yes	No	Tobacco	…
Singh et al (15)[29]	2012	59/M	Pons	Yes	No	Hypertension, previous stroke	…
Singh et al (16)[29]	2012	61/M	Left PCA	Yes	No	Previous stroke	Stroke
Singh et al (17)[29]	2012	63/M	Left MCA branch	Yes	No	Hypertension, previous stroke	…
Smaoui et al[30]	2014	42/M	Left frontal lobe	Yes	No	None specified	…
Terceno et al[31]	2013	37/M	Bilateral MCA and PCA infarctions	No	Yes	Unclear	…
Termote et al[32]	2007	27/M	Left mesencephalon	Unclear	Yes	Alcohol, tobacco	…
Trojak et al[33]	2011	24/M	Insular mantle, lenticular and caudate nuclear structures	Yes	Yes	None	…
Tsivgoulis et al[34]	2014	42/M	Left putamen	Yes	Yes	None	…
Wolff et al (1)[35]	2011	21/M	Vertebrobasilar	Yes	Yes	Unclear	…

(*Continued*)

Table. Continued

Report	Year Published	Age, y/Sex	Territory of Infarct	Temporality	Other Causes of Stroke Excluded	Concomitant Stroke Risk Factors	Subsequent Re-exposure and Effect
Wolff et al (2)[35]	2011	19/M	Vertebrobasilar	Yes	Yes	Unclear	…
Wolff et al (3)[35]	2011	24/F	Vertebrobasilar	Yes	Yes	Unclear	…
Wolff et al (4)[35]	2011	31/F	Anterior circulation	Yes	Yes	Unclear	…
Wolff et al (5)[35]	2011	37/M	Vertebrobasilar	Yes	Yes	Unclear	…
Wolff et al (6)[35]	2011	26/F	Vertebrobasilar	Yes	Yes	Unclear	…
Wolff et al (7)[35]	2011	31/M	Anterior circulation	Yes	Yes	Unclear	…
Wolff et al (8)[35]	2011	44/M	Anterior circulation	Yes	Yes	Unclear	Stroke
Wolff et al (9)[35]	2011	29/M	Vertebrobasilar	Yes	Yes	Unclear	…
Wolff et al (10)[35]	2011	21/F	Vertebrobasilar	Yes	Yes	Unclear	…
Zachariah (1)[36]	1991	34/M	Right basal ganglia and frontoparietal	Yes	Yes	Tobacco	Worsened deficit
Zachariah (2)[36]	1991	32/M	Left basal ganglia and parietal lobe	Yes	Yes	Tobacco	…

ACA indicates anterior cerebral artery; LSD, lysergic acid diethylamide; MCA, middle cerebral artery; and PCA, posterior cerebral artery.

Discussion

This review suggests that the case reports linking cannabis with acute stroke are relatively robust, with high rates of temporality, exclusion of other causes of stroke, and substantial stroke recurrence in patients who resumed cannabis consumption during follow-up. In half, there were concomitant risk factors, such as tobacco and alcohol consumption. However, even if all criteria were met, only a prospective epidemiological study could prove a causal association.

Two epidemiological studies have studied this association. In a large study of hospital admissions in Texas, cannabis exposure was associated with ischemic stroke even after adjusting for alcohol and tobacco (adjusted odds ratio, 1.76; 95% confidence interval, 1.15–2.71).[37] Second, in a prospective case–control study with adjustment for age, sex, and ethnicity, cannabis was associated with the composite of cerebrovascular events (odds ratio, 2.30; 95% confidence interval, 1.08–5.08).[38] Yet after further adjustment for tobacco, the association was weakened (odds ratio, 1.59; 95% confidence interval, 0.71–3.70).

A recent French pharmacovigilance study of cannabis complications detected 3 cerebral complications among a pool of 35 cardiovascular-related cases of cannabis toxicity reported to a central network.[39] The 3 cerebral complications were acute cerebral angiopathy, transient cortical blindness, and spasm of the cerebral artery. Although these 3 cases recovered, there was an overall mortality rate of 25.6% for cardiovascular complications related to cannabis.

Given broad exposure to cannabis in the general population, it is striking that more strokes do not occur among cannabis users. There may be modulation by dose, frequency, strength (% tetrahydrocannabinol), genetic susceptibility, and coingestants. It is possible that exposure is not mentioned by patients with stroke in emergency departments, or that such exposure is overlooked. Overall, however, it seems clear that physiological, clinical, and epidemiological data converge on an increased stroke risk from cannabis exposure. Heightened clinician awareness of this association, particularly in the treatment of young adults, is necessary for preventing recurrent events from future re-exposure to cannabis.

Disclosures

None.

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