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Illicit Drugs and Reversible Cerebral Vasoconstriction Syndrome

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Abstract

Reversible cerebral vasoconstriction syndrome (RCVS) is a condition characterized by thunderclap headache and associated vasospasm of the cerebral vasculature. A multitude of factors are considered to potentially predispose to the development of RCVS. These potential precipitants include numerous illicit drugs. In this study, we investigated the role of illicit drugs as a precipitating factor for RCVS, through systematic review of the relevant literature. We found the strongest evidence for cannabis, but a relative lack of evidence to support other illicit drugs, particularly as individual precipitating factors. We also identified a lack of the consistent application of diagnostic criteria for RCVS, which undoubtedly hampers advancement of knowledge in this field. Consistent adherence to diagnostic criteria will be important for future studies. Ultimately, a prospective registry of RCVS cases would be advantageous to advance understanding of the condition and its underlying causes.

Keywords

reversible cerebral vasoconstriction syndrome, cerebrovascular disorders, headache disorders

Introduction

Reversible Cerebral Vasoconstriction Syndrome (RCVS) is now a well-recognized cause of thunderclap headache. It was formally defined in 2007, unifying a number of conditions under a single set of diagnostic criteria (see Figure 1). The majority of patients experience isolated headache, however associated focal deficits and seizures are also reported in some cases. The condition is generally self-limiting and the majority of patients exhibit resolution of angiographic abnormalities within a matter of weeks. This reversibility should be demonstrated on follow-up angiography within 12 weeks of clinical onset as part of the diagnostic criteria (Figure 1).

RCVS remains poorly understood with respect to its etiology and pathophysiology. The condition can occur spontaneously, but a majority of cases of RCVS appear to be related to particular precipitants.[1,2] These are diverse and appear to lack a common pathophysiological pathway. Over half of the recorded cases have been attributed to the post-partum period or to the prior exposure to vasoactive substances.[1] A majority of the literature repeatedly implicates 3 principal groups of vasoactive drugs, namely serotonergic anti-depressants, triptans, and an array of illicit drugs.[1,2] To our knowledge there has been no previous systematic analysis of the role of illicit drugs as precipitating factors in RCVS.

Methods

We based our search on illicit substances that had been cited as precipitants in previous literature pertaining to RCVS, published between 2007 and 2019. Medline and EMBASE were searched using the following criteria: "Reversible Cerebral Vasoconstriction Syndrome" OR "RCVS" AND "Illicit drugs" OR "Recreational drugs" OR "Cocaine" OR "Amphetamine" OR "Methamphetamine" OR "Crystal Meth" OR "Speed" OR "MDMA" OR "Ecstasy" OR "Marijuana" OR "Cannabis" OR "Khat" OR "LSD" OR "Lysergic Acid Diethylamide" OR "Heroin." References lists were also screened. Previous eponyms for RCVS were excluded from the search in an attempt to align to the diagnostic criteria.[1]

Articles were included in the review if either an original case report or case series, with an explicit diagnosis of RCVS

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1. Acute and severe headache (often thunderclap) with or without focal deficits or seizures
2. Uniphasic course without new symptoms more than 1 month after clinical onset
3. Segmental vasoconstriction of cerebral arteries shown by indirect (eg, magnetic resonance or CT) or direct catheter angiography
4. No evidence of aneurysmal subarachnoid haemorrhage
5. Normal or near-normal CSF (protein concentrations <100 mg/dL, <15 white blood cells per μL)
6. Complete or substantial normalisation of arteries shown by follow-up indirect or direct angiography within 12 weeks of clinical onset

Figure 1. Diagnostic criteria for reversible cerebral vasoconstriction syndrome.[1]

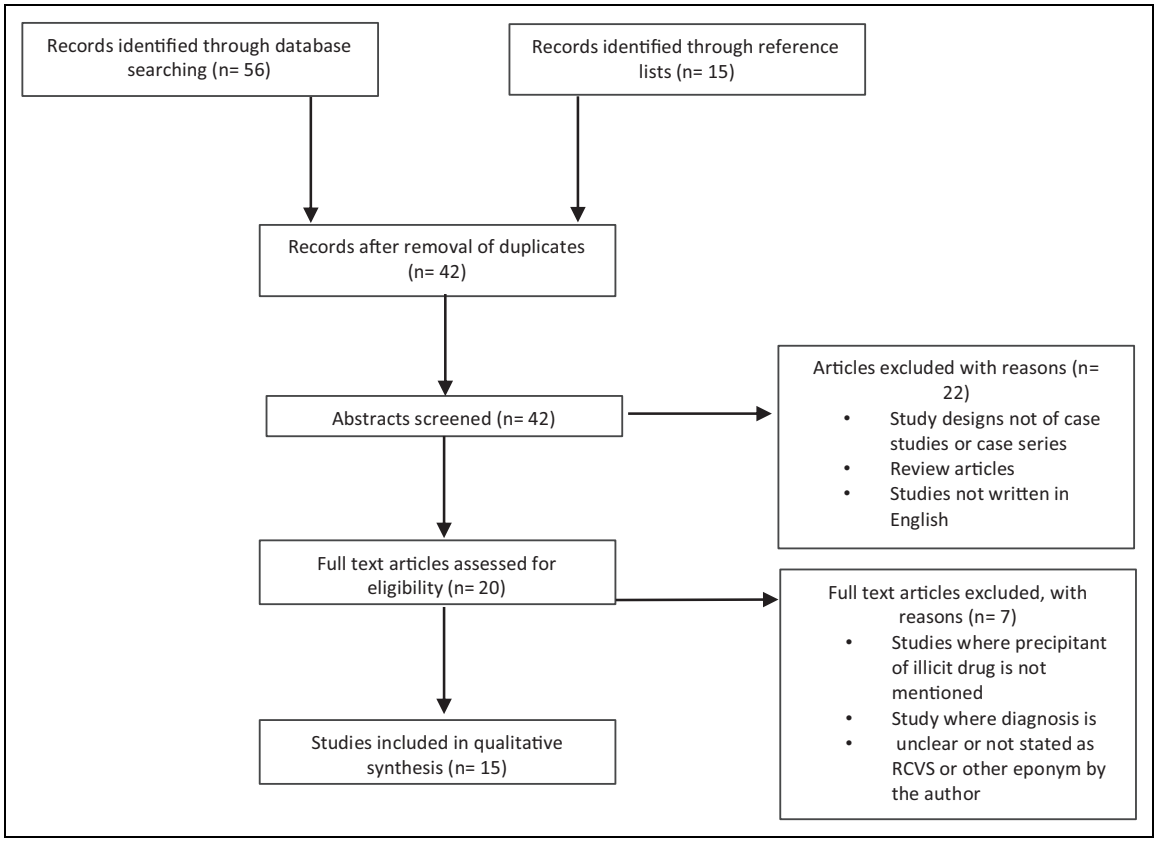

Figure 2. PRISMA flow diagram for selection of case studies/ case series regarding illicit drugs as a precipitant to RCVS.

defined by the author(s). Exclusion criteria included other study designs or review articles, studies with no mention of illicit drug(s) as precipitating factor(s), studies where the diagnosis was unclear or not stated as RCVS or other eponym/ name by the authors, and studies not written in English. A total of 15 papers were included, including 2 large case series.[2,3] This is summarized in Figure 2.

Cases from these papers were included if they observed, and specified, illicit drug exposure as a precipitant factor to the patient developing RCVS. The cases from these papers were collated, with the following variables extracted—age, sex, concurrent precipitant factor (post-partum status or use of another vasoactive substance), type of angiographic imaging used diagnostically, any record of hemorrhagic/ ischemic event, and whether follow up angiography was undertaken. Findings are summarized in Table 1.

Results

A total of 43 cases were identified from the literature, comprising 23 females and 20 males, age range 20-62 years (mean 37.7 years). The Ducros et al. case series (2007) provided almost half of the cases included in this review (20/43). A total of 46% (20/43) of all cases were patients exposed to a single illicit drug preceding RCVS diagnosis, with no concurrent use of vasoactive substances and a negative post-partum status. Of the 15 papers included in this review, 14 used a form of cerebral angiography (either MRA, CTA or DSA) to diagnose RCVS.[2,4,5,6-16] The Jensen et al. case series (2018) was the only report not to explicitly state the imaging modality used for diagnosis.[3] Reversal of the angiographic changes was observed by MRA, CTA or DSA in 29 of 43 cases (67%).[2,5,6,7,9,10,13,15,16] Of these, 23 were undertaken at the 3-month time point, as prescribed by the diagnostic criteria (Figure 1).[2,6,15,13]

Table 1. Results of Literature Search.

Attributed illicit drug(s)	Number of patients	Sex	Age	Concurrent vasoactive substance OR post-partum?	Type of angiographic study	Hemorrhagic or ischemic events noted?	Reversibility shown in follow up angiography?
Cannabis[2]	9	M (1) F (8)	N/A*	No	MRA	Not case specific	Yes, 3 months
Cannabis[2]	4	M (4)	N/A*	Binge drinking	MRA	Not case specific	Yes, 3 months
Cannabis[2]	2	F (2)	N/A*	Nasal decongestant	MRA	Not case specific	Yes, 3 months
Cannabis[2]	1	M	N/A*	SSRI + binge drinking	MRA	Not case specific	Yes, 3 months
Cannabis[2]	1	M	N/A*	Interferon + SSRI	MRA	Not case specific	Yes, 3 months
Cannabis[4]	1	M	46	No	MRA	Ischemic bilateral lesions	Not undertaken, follow up MRI showed improved appearance
Cannabis[5]	1	F	62	SSRI	MRA + DSA	SAH, ICH	Yes, 4 months
Cannabis[3]	1	M	20	No	Not specified	SAH	Not undertaken
Cannabis[3]	1	M	20	No	Not specified	SAH	Not undertaken
Cannabis[3]	1	M	23	No	Not specified	None	Not undertaken
Cannabis[3]	1	F	59	No	Not specified	SAH, IS	Patient died
Cannabis[6]	1	F	53	No	DSA	SAH	Yes, 12 days, however patient died
Cannabis[6]	1	F	23	No	MRA/CTA/DSA	Not specified	Yes, 3 months
Cannabis[7]	1	M	59	No	CTA	Unilateral infarctions in left thalamus and left parietal lobe posteriorly	Yes, day 4
Cannabis[8]	1	M	33	No	DSA	Occipital infarction	Not undertaken
Cannabis[9]	1	F	32	SSRI (Paroxetine)	MRA, CCA	None	Yes, 2 weeks
Cannabis[10]	1	F	53	SSRI (fluoxetine)	MRA, DSA	None	Yes, 2 months
Cocaine[11]	1	F	36	No	MRA	Extracranial 4 vessel dissection	Not undertaken
Ecstasy[12]	1	F	34	Post-partum	MRA	No	Not undertaken (MRA at 1 month showed no resolution)
Khat[13]	1	F	35	Post-partum	MRA	Frontal lobe infarction	Yes, 3 months
Khat[14]	1	M	26	MAO inhibitor (tranylcypromine)	CTA, MRA, DSA	SAH	Not undertaken, follow up MRI
Methamphetamine[3]	1	F	50	SSRI (citalopram)	Not specified	SAH, ICH, IS	Not undertaken
Methamphetamine[3]	1	F	32	SSRI (fluoxetine)	Not specified	SAH, ICH	Not undertaken
Cannabis + cocaine[2]	1	M	N/A*	No	MRA	Not case specific	Yes, 3 months
Cannabis + cocaine[2]	2	M (2)	N/A*	Binge drinking	MRA	Not case specific	Yes, 3 months
Cannabis +cocaine[16]	1	M	52	Pseudoepinephrine	MRA	PRES	Yes, 1 month
Cannabis + methamphetamine[3]	1	F	38	No	Not specified	SAH	Not undertaken
Cannabis +cocaine +ecstasy[3]	1	M	30	SSRI (fluoxetine); lorazepam	Not specified	SAH	Not undertaken
Cannabis + ecstasy + methamphetamines[15]	1	F	23	No	DSA	SAH	Yes, 3 months
Cannabis + amphetamine + methamphetamines[5]	1	M	27	No	CTA, DSA	Convexity SAH	Not undertaken, only clinical follow up

F, female; M, male; SSRI, selective serotonin reuptake inhibitor; MAO inhibitor, monoamine oxidase inhibitor; MRA, magnetic resonance angiography; CTA, computerized tomography angiography; DSA, digital subtraction angiography; SAH, subarachnoid hemorrhage; ICH, intracerebral hemorrhage; IS, ischemic stroke; PRES, Posterior reversible encephalopathy syndrome. * Mean age for participants in this study was 42 years (individual age was not reported in this study).[2]

Cannabis

By far the most common illicit substance reported in the literature was cannabis. Thirty-six cases observed prior exposure to cannabis, with 18 cases recording cannabis as the sole precipitating factor leading to RCVS.[2,3,4,6-8]

Cocaine

There were 6 cases reporting cocaine as a precipitant to RCVS. Just one case was recorded where cocaine was a single precipitant.[11] This patient, a 36-year-old female, exhibited extracranial 4 vessel dissection on angiography. Her symptoms did not resolve prior to discharge, and with 3-month follow up undertaken, reversibility of vasoconstriction was not confirmed; thereby indicating this case did not fulfill diagnostic criteria. The 5 other cases where cocaine was a precipitant also noted concurrent use of another vasoactive substance, including cannabis,[2,3,16] ecstasy,[3,15] binge drinking,[2] selective serotonin reuptake inhibitors (SSRI)[3] and pseudoepinephrine.[16]

Amphetamines and Methamphetamines

Five cases were reported to have methamphetamine as a precipitant to RCVS,[5,3,15] and one case of amphetamines (which were taken concurrently with methamphetamines[5]). There were no cases where methamphetamine was observed as a single precipitant to RCVS, as it was always taken alongside cannabis, ecstasy, amphetamine or an SSRI.

Ecstasy

Ecstasy was implicated as a precipitant in 3 cases.[5,15,12] In 2 of these, ecstasy was taken alongside other illicit substances (cannabis and cocaine/methamphetamines).[5,15] In the third case, the drug was taken by a 34-year-old female who was 1-month post-partum and experiencing sexual headaches.[8]

Khat

Two studies implicated khat as a precipitant to RCVS.[13,14] In the first, a 35-year-old post-partum female presented to the emergency department 10 days after giving birth to her 10th child.[13] In the second, khat was used alongside a monamine oxidase inhibitor.[14] Here, RCVS was diagnosed via DSA in a 26-year-old male, who exhibited associated subarachnoid hemorrhage (SAH).

LSD and Heroin

Despite both of these substances being implicated as precipitants in previous literature,[1,2,17] the current study was unable to identify any evidence of Lysergic Acid Diethylamide (LSD) or heroin as a precipitant to RCVS.

Discussion

Despite a wide variety of illicit drugs being implicated in the development of RCVS,[1,2,17] this study was unable to corroborate a role for most substances. Aside from cannabis, there was a distinct lack of evidence for other illicit drugs (cocaine, ecstasy, amphetamine, methamphetamine, khat), particularly as single precipitating factors. In the case of heroin and LSD,[1,2,17] we found no evidence of them having been implicated in any confirmed cases of RCVS.

The evidence was most abundant for cannabis as a precipitant to RCVS, with many case studies reporting the substance as a single agent in the development of the condition. The link between cannabis and RCVS has been previously described and appears well accepted.[3] The vasoactive nature of cannabis has been well documented pharmacologically in terms of its link to cardiovascular disease, and a temporal relationship has also been found between exposure and ischemic stroke.[18] However, there is a lack of epidemiological evidence to support a causal relationship with RCVS, and no pathophysiological mechanism has thus far been proposed, so this is a direction for future research. With the increasing uptake of medicinal cannabis, as well as artisanal forms such as CBD (cannabidiol) oil for therapeutic purposes it is important to better understand the role of cannabis as a precipitant for RCVS, as well as its potential interaction with other possible precipitating factors.

The evidence for other illicit drugs as precipitating factors was unconvincing for a number of reasons. First, the drug of interest had been often been taken alongside other well-defined precipitants such as cannabis and SSRIs. In some cases, the patient was post-partum, another accepted precipitant of the condition. There was just one study reporting an illicit drug aside from cannabis, as a single precipitant to the development of RCVS.[11] However, a 3-month follow up angiography was not undertaken in this case, which undermines the diagnosis of RCVS.

This study represents a robust systematic review of the available evidence pertaining to illicit drugs as a precipitant to RCVS. Limitations include inherent sources of bias, including the reliance on patient reporting of illicit drug exposure, as well as potential incomplete case reporting and publication bias. Of the cases which reported findings of associated cerebral events, 81% of patients exhibited a hemorrhagic or ischemic event. This is comparable with the upper end noted in previous literature,[1] which may indicate a publication bias toward cases with higher morbidity.

Issues were also highlighted in the consistency of reporting of RCVS, which caused a high level of heterogeneity between case reports. There was inconsistency in the undertaking of follow-up imaging for confirmation of reversibility. This indicates a lack of global adherence to the diagnostic criteria.

It is recommended that awareness and adherence to the diagnostic criteria is increased in order to increase consistency in reporting of RCVS. More contemporaneous and

standardized reporting of illicit drug exposure is also required to specifically understand their role as a precipitant. It has previously been suggested that all patients admitted for a diagnosis of RCVS should undergo a urine toxicology screen[17] which should increase awareness of cases involving illicit drugs. A prospective, potentially international, RCVS case registry could also be considered, which should serve to improve reporting and also consistency, and thereby advance knowledge in this field.

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