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Review

Strokes are possible complications of cannabinoids use☆

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ABSTRACT

It is critically important to identify all factors that may play a role in the recent increase of the incidence of stroke among the young population. Considering the worldwide use of cannabinoids (cannabis and synthetic cannabinoids), the recent legalization of their consumption in some countries, and their supposed involvement in cardiovascular events, we evaluated their role in the occurrence of neurovascular complications among the young.
Ninety-eight patients were described in the literature as having a cannabinoids-related stroke (85 after cannabis use and 13 after synthetic cannabinoids). The distribution by type of stroke was as follows: 4 patients with an undetermined type of stroke, 85 with an ischemic stroke and/or a transient ischemic attack, and 9 with a hemorrhagic stroke. The mean age of patients was 32.3 ± 11.8 years (range 15–63), and the majority of them were male with a sex ratio of 3.7:1. Cannabis was often smoked with tobacco in 66% of cases. Most of the patients with cannabinoids-related strokes were chronic cannabis users in 81% of cases, and for 18% of them, there was a recent increase of the amount of cannabis consumption during the days before the occurrence of stroke. Even if the prognosis of stroke was globally favorable in 46% of cases, with no or few sequelae, 5 patients died after the neurovascular event.
One striking element reported in the majority of the reports was a temporal relationship between cannabinoids use, whether natural or synthetic, and the occurrence of stroke. However, a temporal correlation does not mean causation, and other factors may be involved. Cannabis may be considered as a risk factor of stroke until research shows evidence of an underlying mechanism that, alone or in association with others, contributes to the development of stroke. As of today, reversible cerebral vasoconstriction triggered by cannabinoids use may be a convincing mechanism of stroke in 27% of cases. Indeed, despite the widespread use of cannabinoids, the low frequency of neurovascular complications after their use may be due to a genetic predisposition to their neurovascular toxicity in some individuals. Further studies should focus on this point. More importantly however, this low frequency may be underestimated because the drug consumption may not be systematically researched, neither by questioning nor by laboratory screening. Besides this vascular role of cannabinoids in the occurrence of stroke, a cellular effect of cannabis on brain mitochondria was recently suggested in an experimental study. One of the mechanisms involved in young cannabis users with stroke may be the generation of reactive oxygen species leading to an oxidative stress, which is a known mechanism in stroke in humans. It is useful to inform the young population about the real potential risk of using cannabinoids.
We suggest to systematically ask all young adults with stroke about their drug consumption including cannabinoids, to screen urine for cannabis or to include a specific diagnostic test to detect synthetic cannabinoids, and to obtain non-invasive intracranial arterial investigations (i.e. CT-angiography or cerebral MRA) in order to search for cerebral vasoconstriction. However, several questions remained unresolved and further research is still needed to assess the pathophysiological mechanisms involved in young cannabinoids users with stroke.
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1. Introduction

Cannabis is the most frequent illicit recreational drug used around the world; there are 181 million users [1,2]. Cannabis is the common term used for all the psychoactive products processed from the natural plant *Cannabis sativa*, of which tetrahydrocannabinol (THC) is the most important [1]. Besides natural cannabis, there has been an increase in

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consumption of synthetic cannabis (SC) during the last decade. In 2011, the Drug Enforcement Administration (DEA) categorized 5 synthetic cannabinoids (JWH-018, JWH-073, JWH-200, CP-47497 and [C8]CP-47497) as Schedule I substances under the Controlled Substances Act [3]. These SC, also named spice, K2 or Kronic, are cannabinoids obtained from a laboratory and which are consumed alone or in combination with natural cannabis [4]. In light of the literature in this field, it clearly appears that all the potential harmful effects of marijuana were not taken in consideration when legalizing its use for medical or recreational purposes (respectively in 23 and 4 states in the USA) [5,6], and the current debate in Europe is embarking upon the same path. Indeed, although cannabis is considered by many consumers as safe, several cardiovascular complications are reported in the literature [7–11]. Nonetheless, a recent report published by the World Health Organization (WHO) described that chronic cannabis use may be associated with the occurrence of myocardial infarction or stroke [12]. However, it was also stated that further research is needed to assess the pathophysiological mechanisms involved [12].

Stroke is considered as the main cause of acquired disability and also as the third cause of death among developed countries. It occurs in patients older than 65 years in 75% of cases [13]. Young people (defined as an age under 40, 45, 50 or 55 years depending on different studies), may account for 10% of all patients with stroke [14]. However, a 25% increase of the incidence of stroke among young adults was described in the past two decades [15]. This increase may be due to lifestyle risk factors such as the consumption of tobacco, alcohol or illicit drugs which are more prevalent in this age range [16].

Considering the widespread use of cannabinoids and the latter epidemiological data, it is therefore justified to evaluate their role in the occurrence of stroke among the young. We aimed to review the different aspects of neurovascular complications of cannabis or SC use and the possible pathophysiological mechanisms involved in these complications as described in the literature.

2. Methods

References for this review were found through the search engine PubMed (NCBI) when screening all articles published until November 2016. We combined terms associated with stroke such as ischemic stroke (IS), intracranial hemorrhage (ICH), subarachnoid hemorrhage (SAH), transient ischemic attack (TIA), and terms associated with cannabis (marijuana, synthetic cannabinoids, K2, spice). Articles were also identified from the authors' own files. Articles published in French, Spanish, and English were reviewed for this article.

3. Results

There were 57 articles relating case reports about cannabinoids-related strokes. Among the 98 patients considered in these studies, 85 used cannabis and 13 used SC. In the following sections, we have described first the characteristics of stroke in cannabis users and in SC users separately with detailed data from studies relating cannabis as a risk factor or a prognosis factor for stroke. Thereafter, the potential mechanisms that may be involved in the occurrence of strokes in users of both forms of cannabinoids are analyzed.

3.1. Cannabis-related strokes

In the literature, cannabis use is defined by a positive history and/or by a positive urinary screening. There were 48 articles with a total of 85 patients relating case reports about cannabis-related strokes [17–64]. Eight review articles were specifically focused on this topic [7,31,41,65–69].

The distribution by type of stroke was as follows: 4 patients with an undetermined type of stroke [17–19], 77 with IS and/or TIA [20–64], and 4 with hemorrhagic stroke [45,58,59].

The mean age of patients was 32.7 ± 12 years (range 15–63), and the majority were male with a sex ratio of 3.7:1 Except for one patient who ingested bhang (which is an edible form of cannabis), all the others had smoked cannabis [64]. The most frequent risk factor associated with the use of cannabis was tobacco in 69% of cases (n = 59), and alcohol use was reported in 29% of cases (n = 25). The other risk factors that are described classically in older people such as hypertension, diabetes, and dyslipidemia were poorly represented in this young population (for details see Table 1). Patients with cannabis-related strokes were chronic cannabis users in 86% of cases (n = 73). For 25% of them (n = 18), there was a recent increase of the amount of cannabis consumption the days before the occurrence of stroke [47]. In 10 cases, there was another illicit drug or a potential vasoactive medication used in combination with cannabis: amphetamines (n = 3) [40,43,59], buprenorphine (n = 2) [45,63], steroid anabolisant (n = 1) [57], serotonergic medication in combination with triptan (n = 2) [47,53] or serotonergic medication alone (n = 2) [59,60].

3.1.1. Ischemic strokes and transient ischemic attack

There were 69 patients described as having a persistent neurological deficit related to an IS [17–42,46–57,60,62–64]. Eight patients had an initial transient neurological deficit that was followed (n = 4) [22,29,43,50] or not (n = 4) by a persistent deficit related to an IS [31,44].

The IS (n = 73) was located in a posterior vascular territory in 37% of cases (n = 27), in an anterior territory in 53.4% of cases (n = 39), and in both anterior and posterior territories in 4% of cases (n = 3). The territory was unspecified in 4 patients.

Reversible cerebral vasoconstriction syndrome (RCVS) was considered as the cause of stroke in 31.5% of cases (n = 23) [33,34,42,47,50,53,60–62]. Among these cases, strokes were located in a posterior territory in 48% of cases (n = 11), in an anterior territory in 30% (n = 7), and in both territories in 13% (n = 3). In two cases, the information concerning the territory was not available. Besides cannabis, another precipitant factor for RCVS was found in 3 patients: serotonergic antidepressant alone (n = 1) [60] or in association with triptan (n = 2) [47,53].

In 12% of cases (n = 9), a recurrence of stroke was described during the follow-up period and all of them had continued their cannabis consumption after the first event.

Among the patients with IS, clinical outcome was favorable in 41% of cases (n = 30) with few or no sequelae. In 40% of cases (n = 29), patients had a significant persistent deficit and 7% (n = 5) died [26,28,48,61]. In 12% of cases (n = 9) the clinical outcome was not specified. Among the 4 patients with TIA, three of them were asymptomatic at discharge and for the last one the outcome was not specified.

3.1.2. Hemorrhagic stroke

In the literature, only 4 patients were described with hemorrhagic stroke related to cannabis use [45,58,59]. Indeed, one author reported the case of a 34-year-old woman with an isolated right temporal lobe ICH [45]. Another case was stated with a left hemisphere ICH associated with two limited IS in the right hemisphere in a 38-year-old man [58]. Two other patients were described as sustaining an isolated convexity SAH (a 27-year-old man and a 62-year-old woman) [59]. The etiology for these hemorrhagic strokes was RCVS for three patients [45,59]. It remained undetermined for one patient [58]. Besides cannabis use, there was another precipitating factor for cerebral vasoconstriction in the three patients with RCVS: use of buprenorphine in one case [45], amphetamines and methamphetamines in another one, and serotonergic antidepressant use in the last one [59]. A recent increase in cannabis use was mentioned for one patient [58]. Clinical outcome was favorable in all the cases, with one patient being symptom-free [45,59], and the three others suffering from minor symptoms [58,59].