Cannabis Use, Ischemic Stroke, and Multifocal Intracranial Vasospasm
A Prospective Study in 48 Consecutive Young Patients

Valérie Wolff, MD; Valérie Lauer, MD; Olivier Rouyer, MD, PhD; François Sellal, MD; Nicolas Meyer, MD, PhD; Jean Sébastien Raul, MD, PhD; Cécile Sabourdy, MD; Fazel Boujan, MD; Christine Jahn, MD; Rémy Beaujeux, MD; Christian Marescaux, MD

Background and Purpose—Our objective was to evaluate the relationship between cannabis use and ischemic stroke in a young adult population.

Methods—Forty-eight consecutive young patients admitted for acute ischemic stroke participated in the study. First-line screening was performed, including blood tests, cardiovascular investigations, and urine analysis for cannabinoids. If no etiology was found, 3D rotational angiography and cerebrospinal fluid analysis were performed. A control was planned through neurovascular imaging within 3 to 6 months.

Results—In this series, there was multifocal intracranial stenosis associated with cannabis use in 21% (n=10).

Conclusions—Multifocal angioopathy associated with cannabis consumption could be an important cause of ischemic stroke in young people. (Stroke. 2011;42:1778-1780.)

Key Words: stroke in young adults ■ vasospasm ■ cannabis

It has been recently reported that cannabis may contribute to acute ischemic cardiovascular or cerebrovascular events.1 This possible effect was researched in a 2-year prospective study with a standardized assessment of all patients younger than 45 years admitted for ischemic stroke (IS).

Methods
From October 2005 to September 2007, 48 consecutive patients younger than 45 years of age who were admitted to our stroke unit for IS were included in this study. Patients were informed that they were included in a prospective study and agreed to participate. Standard T1, T2, FLAIR sequences, diffusion-weighted-imaging magnetic resonance imaging scans were acquired for all patients. Vascular imaging comprised 3D-time of flight magnetic resonance angiography (n=43) or cerebral computed tomography angiography (n=44). Cardiac explorations included electrocardiogram (n=48), transthoracic echocardiography (n=48), and transoesophageal echocardiography (n=29). Exhaustive laboratory analyses were performed for all patients. If first-line investigations were inconclusive, 3D rotational angiography (n=30) and cerebrospinal fluid analysis (n=29) were performed. A questionnaire was used to determine cardiovascular risk factors, history of medication, and illicit drug or alcohol use. Urines were systematically screened for cannabinoids, cocaine,amphetamine, and methylenedioxyamphetamine. Follow-up clinical visits (n=44) and control of vascular imaging (n=20) were planned within 3 to 6 months after discharge from hospital.

One study neurologist and 1 study radiologist separately reviewed all 3D-time of flight or computed tomography angiography images. A single operator performed all 3D rotational angiography, and 2 study radiologists, who were unaware of magnetic resonance angiography results, reviewed the 3D rotational angiography images. Involvement of single or several vessel segments were respectively classified as monoarterial stenosis or as multifocal intracranial stenosis (MIS).

Statistical Analysis
Data are summarized using descriptive statistics. Because of sparseness of data, computations of odds ratio and 95% CI, as well as multivariate logistic regression, were obtained using exact methods (StatXact and LogXact). The logistic regression was designed using the group of MIS as the dependent variable and the other variables as potential predictors. A probability value ≤5% was considered statistically significant.

Results
Table displays the relationship between stroke etiology, classical risk factors, and cannabis use in the 48 patients. There were no patients undergoing serotonergic medical treatment, and there were no amphetamine, methylenedioxy-methamphetamine, or cocaine users. Urine toxic analyses were positive for cannabis only in the 13 patients who admitted to smoking cannabis, and among them, all were
tobacco smokers. Ten of 13 cannabis users displayed a specific pattern of MIS. Nine of these 10 patients had severe headache, and none had thunderclap headache. IS were located in the vertebrobasilar territory in 7 of 10 patients, and MIS predominated in posterior cerebral arteries (9 of 10 patients) and superior cerebellar arteries (7 of 10 patients). Lumbar puncture (8 of 10 patients) and blood analysis showed no significant abnormalities.

The association between MIS and cannabis was highly significant (odds ratio, 113 [9–5047]; P<0.001). Indeed, 10 patients of 11 with MIS were cannabis users. An exact logistic regression showed that no other factor could be introduced in the model, and thus no other factor appeared to be related independently to MIS.

The medical history of these patients strongly supported a temporal link between cannabis use and stroke associated with MIS (Figure). The 10 patients began to smoke cannabis on a regular basis several months to years before stroke onset. During the days before stroke, they all binged on cannabis, and 5 drank an unusually large amount of alcohol. Six patients stopped cannabis use after stroke with a favorable clinical outcome without relapse at 3 to 6 months. Control of

<table>
<thead>
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<th>Total</th>
<th>Extracranial Dissection</th>
<th>Cardioembolism</th>
<th>Monoarterial Intracranial Stenosis</th>
<th>Multifocal Intracranial Stenosis</th>
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<td>6</td>
<td>10</td>
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<td>12</td>
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<td>Cannabis use</td>
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<td>0</td>
<td>1</td>
<td>10</td>
<td>1</td>
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</tbody>
</table>

N indicates number of patients.

Figure. Typical example of the temporal link between cannabis consumption and MIS. Because of his familial history of aneurysm, a cerebral magnetic resonance angiography was performed when he was 19 and was normal (A). At age 20 years, he started smoking cannabis on a weekly basis. At age 21, he was hospitalized for a left cerebellar syndrome associated with unusual headache. Cerebral MRI showed a left cerebellar infarct. Cerebral magnetic resonance angiography disclosed MIS of basilar artery, both posterior cerebral arteries and superior cerebellar arteries (B); that were confirmed on 3D rotational angiography (C). After complete stop of cannabis use, the clinical outcome was favorable. Control cerebral magnetic resonance angiography (D) showed reverse of MIS at 3 months.
vascular imaging showed partial (n=3) or total (n=3) reversibility of MIS. Of the 3 remaining patients who still smoked cannabis, clinical outcome was favorable without relapse in 2, and was unfavorable in 1 patient, who underwent a new IS. At 3 to 6 months, there was no reversibility in these 3 patients.

Discussion
In our prospective cohort of 48 consecutive young patients with IS, 10 patients (21%) displayed a specific pattern of MIS that seemed to be associated with cannabis use. Using exact logistic regression, cannabis use appeared to be the most strongly associated factor with MIS. The 2 main radiological characteristics of their angiopathy were the involvement of multiple intracranial arteries and the reversibility of vasoconstriction after cannabis withdrawal.

Since 1987, fewer than 25 cases of IS associated with cannabis smoking have been published.2,3,4,5,6,7 As in our study, IS were more frequent in vertebrobasilar territory, suggesting susceptibility of posterior circulation.2,3,4 Concomitant alcohol consumption3 or unusually high consumption of cannabis were regarded as possible precipitating factors.3,4,5

Our results raise the question of the relationship between the vasoconstriction pattern and the reversible cerebral vasoconstriction syndrome recently described.7,8 In regards to this study, we have to conclude that cannabis is not as harmless as was thought, and cerebral vascular risk when consumed is probably underestimated.

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Disclosures
None.

References
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大麻の使用、虚血性脳卒中、および多巣性頭蓋内血管収縮—48例の連続する若年患者を対象とした前向き研究

Cannabis Use, Ischemic Stroke, and Multifocal Intracranial Vasoostriction
—A Prospective Study in 48 Consecutive Young Patients

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Abstract

背景および目的: 本研究の目的は、若年成人集団における大麻の使用と虚血性脳卒中の関連を評価することであった。

方法: 急性虚血性脳卒中のために入院した48例の連続する若年患者が本研究に参加した。血液検査、心血管検査、カンナビノイドの尿検査を含む一次スクリーニングを行った。病因が見出されなかった場合は、三次元回転血管造影と脳脊髄液分析を行った。対照は3～6カ月以内の神経血管造影によるものとした。

結果: このシリーズでは、21%（10例）に大麻の使用に関連した多巣性頭蓋内狭窄が認められた。

結論: 大麻の使用に関連した多巣性血管症は若年者における虚血性脳卒中の重要な原因である可能性がある。

Stroke 2011; 42: 1778-1780

図

大麻の使用と多巣性頭蓋内動脈狭窄（multifocal intracranial stenosis: MIS）の関の時間的関連を示す典型例。動脈瘤の家族歴があるため、患者が19歳の時に脳の磁気共鳴血管造影を行い、結果は正常であった（A）。20歳の時に、患者は週1回の頻度で大麻を吸うようになった。21歳の時に、異常な頭痛を伴う左小脳症候群のため入院した。脳のMRIに左小脳梗塞が認められた。脳の磁気共鳴血管造影により、脳底動脈両側、後大脳動脈および上小脳動脈にMISが明らかになった（B）。これは三次元回転血管造影で確認された（C）。大麻の使用を完全に止めたら、臨床転帰は良好であった。対照の脳磁気共鳴血管造影で（D）、3カ月後にMISが解消したことが認められた。