Cannabis, Ischemic Stroke, and Transient Ischemic Attack
A Case-Control Study

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Background and Purpose—There is a temporal relationship between cannabis use and stroke in case series and population-based studies.

Methods—Consecutive stroke patients, aged 18 to 55 years, who had urine screens for cannabis were compared with a cohort of control patients admitted to hospital without cardiovascular or neurological diagnoses.

Results—One hundred sixty of 218 (73%) ischemic stroke/transient ischemic attack patients had urine drug screens (100 men; mean [SD] age, 44.8 [8.7] years). Twenty-five (15.6%) patients had positive cannabis drug screens. These patients were more likely to be men (84% versus 59%; $\chi^2$: $P=0.016$) and tobacco smokers (88% versus 28%; $\chi^2$: $P<0.001$).

Control urine samples were obtained from 160 patients matched for age, sex, and ethnicity. Thirteen (8.1%) control participants tested positive for cannabis. In a logistic regression analysis adjusted for age, sex, and ethnicity, cannabis use was associated with increased risk of ischemic stroke/transient ischemic attack (odds ratio, 2.30; 95% confidence interval, 1.08–5.08). However after adjusting for tobacco use, an association independent of tobacco could not be confirmed (odds ratio, 1.59; 95% confidence interval, 0.71–3.70).

Conclusions—This study provides evidence of an association between a cannabis lifestyle that includes tobacco and ischemic stroke. Further research is required to clarify whether there is an association between cannabis and stroke independent of tobacco.

Clinical Trial Registration—URL: http://www.anzctr.org.au. Unique identifier: ACTRN12610000198022 (Stroke. 2013; 44:2327-2329.)

Key Words: cannabis ■ drug abuse ■ ischemic stroke ■ transient ischemic attack

Cannabis is the most widely used illicit drug of abuse.1 Case reports, case series, and population-based studies have reported an association between ischemic stroke/transient ischemic attack (TIA) and cannabis use.2-5 A causal relationship with cannabis has been suggested by cerebral ischemia developing during or within hours of cannabis reexposure, and recurrent episodes of stroke and TIA after cannabis reexposure.6 We performed a case-control study to explore the relationship between cannabis and stroke.

Methods
Cannabis drug screens were added to the routine investigations of younger ischemic stroke/TIA patients in 2009. Consecutive patients, aged 18 to 55 years, were asked to provide a urine sample within 72 hours of admission. Cannabis was detected using gas chromatography on a 5-mL aliquot of urine. Cannabis levels ≥25 ng/mL indicated a positive result. With the tests used cannabis is detected for 72 hours after single exposure and ≤10 weeks with daily use.

Control participants were admitted under the Internal Medicine Service without cardiovascular or neurological diagnoses and were frequency-matched by age, sex, and ethnicity to the patients. Control urine samples had been provided for other indications. The drug screen result, age, sex, ethnicity, and current tobacco use of each control participant were provided separately to the investigators, who could not trace a result back to a specific patient.

An audit of the first 46 patients found positive cannabis drug screens in 8 (17%) patients. We assumed that 6% of control participants would have positive urine drug screens on the basis of self-reported cannabis use in the general population.6 Using this information, a sample size of 147 stroke patients and 147 control participants (rounded to 160 in each group) was estimated to have an 80% chance of showing a significant difference ($P<0.05$).

Statistical analyses were performed using the STATA 10.0 (College Station, TX). Categorical data were analyzed with the $\chi^2$ statistic, with Fisher exact test used, if the expected cell size was small. Results were considered significant at the 5% level. Logistic regression was used to compute odds ratios and confidence intervals controlling for matching factors, age, sex, ethnicity, and tobacco use. The study was approved by the regional ethics committee and registered with the Australia New Zealand Clinical Trials Registry.

Results
One hundred sixty of 218 (73%) ischemic stroke/TIA patients, aged 18 to 55 years, had urine drug screens between January

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2009 and April 2012 (100 men, 60 women; mean [SD], age 44.8 [8.7] years), of whom 150 (94%) had ischemic stroke and 10 (6%) had TIA (Table 1). All patients approached to provide a urine sample agreed to do so. Fifty-eight patients did not have urine drug screens because they had been admitted outside office hours or were discharged early. There were no baseline or outcome differences between patients with and without drug screens (data not shown). Control urine samples were obtained from 160 patients. The cases and controls were well matched for age, sex, and ethnicity (Table 2).

Twenty-five of 160 (15.6%) patients had cannabis detected in urine drug screens. Patients with positive screens were more likely to be men, Māori, and tobacco smokers and had worse outcome at discharge (Table 1). Thirteen of 160 (8.1%) control participants tested positive for cannabis. In a logistic regression analysis adjusted for age, sex, and ethnicity, cannabis use was associated with increased risk of ischemic stroke/TIA (odds ratio, 2.30; 95% confidence intervals, 1.08–5.08). However after adjusting for current tobacco use, the association between cannabis use and stroke reduced to the null (odds ratio, 1.59; 95% confidence intervals, 0.71–3.70).

Discussion
This study provides evidence of an association between a lifestyle that includes cannabis and tobacco, and ischemic stroke. However, finding an association is not the same as proving causality. Almost all patients with positive cannabis screens used tobacco (which is often mixed with the cannabis and smoked) and an association independent of tobacco was not found.

A causal relationship with cerebral ischemia is plausible as cannabis has cardiovascular effects over and above those of tobacco.7 Cannabis causes a dose-dependent increase in heart rate, supine hypertension, postural hypotension, and an increase in cardiac output.8 The risk of myocardial infarction is elevated 5× over baseline in the hour after cannabis use.9 Cannabis use has been temporally associated with paroxysmal atrial fibrillation and sudden cardiac death.10 Cannabis may lead to reversible cerebral vasoconstriction syndrome11 and multifocal intracranial arterial stenosis.4 Chronic cannabis use is also associated with increased cerebrovascular resistance.12

The strengths of this study include the use of a control cohort. Three quarters of patients had drug screens so that the results can be generalized. However, although matching was successful for age, sex, and ethnicity, other important factors, such as socioeconomic or employment status, and alcohol or other drug use, could not be considered. The choice of the control patients is also another potential source of bias. The need to maintain anonymity meant that extensive comparisons between patients and controls were not possible.

Cannabis is generally perceived as having few serious adverse effects. This study suggests that this may not be the

Table 1. Comparison of Ischemic Stroke and Transient Ischemic Attack Patients With and Without Positive Cannabis Urine Drug Screens

<table>
<thead>
<tr>
<th></th>
<th>Cannabis Positive, n (%)</th>
<th>Cannabis Negative, n (%)</th>
<th>Total, n (%)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Men:women</td>
<td>21:4</td>
<td>79:56</td>
<td>100:60</td>
<td>0.016*</td>
</tr>
<tr>
<td>Age, mean (SD), y</td>
<td>43.2 (9.1)</td>
<td>45.1 (8.6)</td>
<td>44.8 (8.7)</td>
<td></td>
</tr>
<tr>
<td>Ethnicity</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>European New Zealand</td>
<td>13 (52)</td>
<td>75 (56)</td>
<td>88 (55)</td>
<td></td>
</tr>
<tr>
<td>Māori</td>
<td>10 (40)</td>
<td>9 (7)</td>
<td>19 (12)</td>
<td></td>
</tr>
<tr>
<td>Pacific</td>
<td>1 (4)</td>
<td>24 (18)</td>
<td>25 (16)</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>1 (4)</td>
<td>27 (20)</td>
<td>28 (18)</td>
<td>&lt;0.001†</td>
</tr>
<tr>
<td>Ischemic stroke</td>
<td>23 (92)</td>
<td>127 (94)</td>
<td>150 (94)</td>
<td></td>
</tr>
<tr>
<td>Transient ischemic attack</td>
<td>2 (8)</td>
<td>8 (6)</td>
<td>10 (6)</td>
<td></td>
</tr>
<tr>
<td>Stroke mechanism</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Large artery atherosclerosis</td>
<td>1 (4)</td>
<td>9 (7)</td>
<td>10 (6)</td>
<td></td>
</tr>
<tr>
<td>Small vessel occlusion</td>
<td>2 (8)</td>
<td>13 (10)</td>
<td>15 (9)</td>
<td></td>
</tr>
<tr>
<td>Cardioembolism</td>
<td>4 (16)</td>
<td>35 (26)</td>
<td>39 (24)</td>
<td></td>
</tr>
<tr>
<td>Undetermined</td>
<td>14 (56)</td>
<td>57 (42)</td>
<td>71 (44)</td>
<td></td>
</tr>
<tr>
<td>Other determined</td>
<td>4 (16)</td>
<td>21 (16)</td>
<td>25 (16)</td>
<td>0.790†</td>
</tr>
<tr>
<td>Risk factors</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>10 (40)</td>
<td>54 (40)</td>
<td>64 (40)</td>
<td>1.000*</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>12 (48)</td>
<td>64 (47)</td>
<td>76 (48)</td>
<td>0.691*</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>5 (20)</td>
<td>23 (17)</td>
<td>28 (18)</td>
<td>0.454†</td>
</tr>
<tr>
<td>Current smoking</td>
<td>22 (88)</td>
<td>38 (28)</td>
<td>60 (36)</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>2 (8)</td>
<td>12 (9)</td>
<td>14 (9)</td>
<td>0.622†</td>
</tr>
<tr>
<td>Ischemic heart disease</td>
<td>1 (4)</td>
<td>6 (4)</td>
<td>7 (4)</td>
<td>0.700†</td>
</tr>
<tr>
<td>Discharge mRS (median)</td>
<td>3</td>
<td>1</td>
<td>4</td>
<td>0.036</td>
</tr>
</tbody>
</table>

mRS indicates modified Rankin Scale.
*χ² test; and †Fisher exact test.
future research should attempt to determine whether there is an association between cannabis and stroke that is independent of tobacco use. This may prove difficult given the risks of bias and ethical strictures of studying an illegal substance. However, the high prevalence of cannabis use in this cohort of younger stroke patients makes this research imperative.

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Disclosures
None.

References
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