CANNABIS CONSUMPTION AND THE RISK OF PSYCHOSIS

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Summary

Objectives: Cannabis is the most widely used illicit drug globally and its use has been linked to an increased risk for psychotic disorders. An association between cannabis consumption and psychotic symptoms was consistently reported by several studies. This case-control study aimed to widen the current findings about the impact of cannabis exposure on the risk of psychosis, by investigating the pattern of cannabis consumption in a sample of first-episode of psychosis (FEP) patients compared to healthy controls.

Material and methods: 68 individuals who presented for the first time to mental health services of Palermo (Italy) with an ICD-10 diagnosis of psychotic disorders and 74 healthy were enrolled as part of the Sicilian Genetics and Psychosis study. Psychopathological assessment and diagnosis were carried out by the Schedule for Clinical Assessment in Neuropsychiatry (SCAN). Socio-demographic data were collected by the modified version of the Medical Research Council (MRC) socio-demographic scale. All participants were interviewed using the Cannabis Experience Questionnaire – Modified Version to obtain a detailed assessment of lifetime patterns of cannabis and other illicit drug consumption. Logistic regression was applied to investigate the relationships between various aspects of cannabis use (lifetime use, age at first use, duration, and frequency of use) and case-control status while controlling for potential confounders.

Results: Patients started cannabis consumption about 3 years earlier than the control group (t = 3.1, p = 0.002) and were 8 times more likely to having started using cannabis before 15 years (adjusted OR = 8.0, 95% CI 2.4-27) than controls. Furthermore cases were more likely to smoke more frequently than controls (adjusted OR = 4.4, 95% CI 1.08-18). We did not find a difference in duration of cannabis use between cases and controls.

Conclusions: The findings suggest that cannabis exposure, and especially daily cannabis consumption, is associated with the risk for psychosis; however, the retrospective study design does not allow drawing firm conclusions about causality.

Key words: cannabis, schizophrenia, psychosis, tetrahydrocannabinol, drug and schizophrenia

Introduction

Cannabis exposure has been associated to an increased risk of developing psychosis. Cannabis is the most popular illicit drug worldwide, and although most people who smoke cannabis do not become psychotic, evidence from the literature supports an association between cannabis use and an increased risk of developing a psychotic disorder [1,2].

The main psychoactive component, which is responsible of the psychotogenic effect of cannabis, is Δ9-tetrahydrocannabinol (Δ9-THC). The other main constituent of cannabis is cannabidiol (CBD) which has antianxiety and antipsychotic properties [3,4]. Recently, high potency varieties of cannabis, such as "skunk" (*sensimilla*), have become available in the market over much of Europe. Such varieties of cannabis contain a high concentration of THC and a lower proportion of CBD which seems

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to "balance" the psychotogenic effect of the former [3 4]. Cannabis intoxication can cause brief psychotic episodes or may exacerbate pre-existing psychotic symptoms [5 6]. It has been shown that healthy people who are administered THC intravenously were more likely to develop transient psychotic-like experiences and that THC worsens psychotic symptoms in people suffering from psychosis [7]. THC exerts its psychotogenic role by modulating the dopamine neurotransmission, which is involved in development of psychotic symptoms.

The first report suggesting that cannabis might be a risk factor for psychosis was the Swedish Conscript study. This was a 15 year follow-up of a cohort of 45.570 conscripts into the armed forces. The risk of schizophrenia was 2.3 fold higher among subjects who had used cannabis by 18 years and there was a dose response relationship, as the risk of developing schizophrenia was even higher in those who had smoked cannabis more frequently [8]. Subsequently, a series of cohort studies have shown that cannabis use generally predates psychosis [9-13]. For instance, the Dunedin cohort study reported that children and adolescents who had used cannabis by the age of 15 years were 4.5 times more likely to develop schizophreniform psychosis at the age of 26 years [9]. van Os et al. reported a three times higher risk of developing psychotic symptoms in the general population associated to cannabis consumption [12]. Two meta-analyses concluded that cannabis consumption was associated with approximately two-fold increased risk of developing a psychotic disorder [1 2].

Individuals who showed any evidence of psychosis proneness appear especially vulnerable, as those who started using cannabis in early adolescence. A meta-analysis by Large et al. supported the association between cannabis consumption and an earlier age at first presentation of psychosis [14]. Other studies confirmed that cannabis use is associated to an earlier age at first presentation of schizophrenia and that there is an interaction between cannabis use and gender difference in age at first presentation, in the way that the difference by gender in age at first presentation is reduced in cannabis users [15]. Furthermore, recent evidence shows that high potency cannabis and higher frequency of use are associated with a higher risk of developing psychosis [3].

However, only a small proportion of cannabis users develop psychotic symptoms or schizophrenia. Cannabis users who develop psychosis may have an underlying genetic susceptibility, and some gene polymorphisms have been associated to an increased risk to develop psychosis [16-21]; nevertheless, these results need to be further replicated.

Materials and methods

The Sicilian Genetic and Psychosis (SGAP) study is an incidence and a case-control study, carried on by the Psychiatric Section of Palermo University Department of Experimental Biomedicine and Clinical Neurosciences (BioNeC), aimed at identifying the role of putative genetic and environmental risk factors for psychosis, including cannabis.

In this work the focus will be on the impact of cannabis exposure on the risk of psychoses. Specifically, we aimed to compare patterns of cannabis consumption between cases and controls (exposure to cannabis lifetime, age at first use, duration of cannabis consumption, total number of times used, frequency of use) and to discuss the impact of cannabis exposure on psychosis risk in Palermo.

Participants

A screening of cases aged between 18-65 years affected by any psychoses was run on all the subjects presenting to the mental health services of Palermo with a first-episode of psychosis (FEP) in a three-year period. 204 patients at their first-episode of psychosis (defined as the first contact with psychiatric services) were identified.

Inclusion criteria for cases were:

- presence of symptoms of any psychosis such as delusions, hallucinations, thought disorder, bizarre or disturbed behaviour, negative symptoms, mania;
- residence in Palermo;
- first ever contact with psychiatric services for psychotic symptoms;
- age between 18 and 65 years;
- absence of an organic cause of psychosis and severe learning disability;
- diagnosis of ICD-10 criteria for schizophrenia (F20), other non-affective psychoses (F21-29) or affective psychoses (F30-33).

Cases were excluded if they met any of the following criteria:

- presence of an organic cause underlying psychotic symptoms;
- previous contact with mental health services for an episode of psychosis;
- age under 18 or over 65;
- presence of psychotic symptoms resulting from acute intoxication as defined by ICD-10 criteria.

A case control analysis was performed in a subsample of 68 cases (out of the 204 identified for the incidence study) that were compared to 74 healthy controls. The control sample was recruited from the same catchment area as cases, through leaflet distributions and Internet and newspaper advertisements, and was representative of the general population at risk for the disease.

Measures

The assessment of cases was performed by the following instruments:

- the Schedule for Clinical Assessment in Neuropsychiatry (SCAN) [22] was used to assess psychopathology and to define the diagnosis of psychosis;
- a modified version of the MRC Socio-demographic Schedule [23] adapted to the Italian context was used to collect socio-demographic data (age, gender, ethnicity, level of education, and occupational status);
- the Cannabis Experience Questionnaire – Modified Version (CEQmv) [3] was administered to collect data on cannabis and other illicit drugs consumption. The questionnaire explores cannabis consumption in details, including: age at first use, lifetime cannabis consumption, current cannabis consumption (defined as cannabis consumption within the four weeks before the assessment), frequency of use, duration of use in years (more or less than 5 years), other drugs consumption (including all illicit drugs, among which stimulants, tobacco, and alcohol).

Controls were administered the same instruments as cases except the SCAN and they were asked to complete the Psychosis Screening Questionnaire (PSQ) [24] to exclude the presence of a current or past psychotic disorder.

Ethics

The study was approved by the Ethical Committee of the Palermo University Medical School and the data collection in the mental health services has been authorized by the Department of Mental Health of Palermo which coordinates all the psychiatric services involved in the study. The work has been performed in accordance with the principles of the 1983 Declaration of Helsinki. Study participants were asked to sign a consent form before attending the interview.

Analyses

Patterns of cannabis use in cases and controls were investigated using, where appropriate, $\chi 2$-test or Fisher exact test (cannabis use lifetime, current cannabis use, frequency of cannabis use, use before and after 15 years). Welch test and Wilcoxon tests were used to calculate mean age at first use and mean duration of cannabis use for cases and controls because of unequal variances. ANOVA was used to evaluate differences in the mean age of first cannabis consumption by case-control status. Logistic regression was used to analyze the association between the pattern of cannabis use and the risk of psychosis, controlling for possible confounders. Confounders were selected as the main socio-demographic differences between cases and controls that might influence the risk of psychosis (age, gender, level of education, occupational status, psychiatric family history, and other drug use).

Results

Socio-demographic characteristics of cases and controls are displayed in Table I.

Table II summarizes differences in patterns of cannabis consumption between cases and controls. In Palermo sample, patients were not more likely than controls to have smoked cannabis at least once, lifetime (OR = 0.4, 95% CI 0.1-1.1) and this may reflect that cannabis consumption is quite spread in the general population. No differences in lifetime cannabis consumption by gender both in cases ($\chi 2 = 1.4$, df = 1, p = 0.238) and controls ($\chi 2 = .8$, df = 1, p = 0.178) were found.

After adjusting for possible confounders (age, gender, education, occupational status, psychiatric family history, and other drugs abuse) cases were over 5 times (adjusted OR = 5.4 ,95% CI 1.2-24.1) more likely than controls to be current cannabis consumers (meaning having smoked cannabis in the previous four weeks). In addition, mean age at first use of cannabis differed between cases and controls. Patients started cannabis consumption about 3 years earlier than controls (Welch test t = 3.1, df = 60, p = 0.002).

Accordingly to the existing literature, age of 15 years old might be a critical age of first exposure [25 26]; therefore, we investigated the odds of being a case having been exposed to cannabis “before 15 years of age”. We found that cases were 8 times more likely than controls to having started using cannabis before 15 years (adj. OR = 8, 95% CI 2.4-27).

Furthermore, previous literature on cannabis exposure in FEP patients reported that cases were about six times more likely than controls to use cannabis every day [3]. In Palermo sample, frequency of cannabis consumption in cannabis users was coded as

Table I. Sample characteristics of cases and controls.

	Cases (n = 68)	Controls (n = 74)	p*
Age, years mean (sd)	28.25 (11.2)	36 (13.2)	**< 0.001**
Median (IQR)	24 (13)	33.5 (28)	
No details	-	-	
Gender, n (%)			
Male	44 (64.7)	39 (52.7)	0.147
Female	24 (35.3)	35 (47.3)	
No details	-	-	
IQ (WAIS) mean (sd)	78.71 (16.81)	101.58 (23.05)	**< 0.001**
No details	34	-	
Migration status, n (%)			
Natives	60 (88.2)	70 (94.6)	0.174
Migrant	8 (11.8)	4 (5.4)	
No details	-	-	
Ethnicity, n (%)			
Caucasian	64 (94.1)	71 (95.95)	0.710
Non Caucasian	4 (5.9)	3 (4.05)	
No details	-	-	
Level of education, n (%)			
No education	0	2 (2.7)	**< 0.001**
Primary school	9 (13.4)	1 (1.4)	
Junior High	26 (38.8)	13 (17.8)	
Diploma	30 (44.8)	47 (64.4)	
University	2 (3)	10 (13.7)	
No details	1	1	
Mean age left education, sd	16 (2.91)	19.3 (3.5)	**< 0.001**
No details	1	1	
Employment, n (%)			
Unemployed	41 (61.2)	17 (23)	**< 0.001**
Employed	14 (20.9)	35 (47.3)	
Student	12 (17.9)	11 (14.9)	
Retired	0	11 (14.9)	
No details	1	-	
Relationship status, n (%)			
In a stable relationship	14 (20.6)	47 (63.5)	**< 0.001**
Single/separated/divorced	54 (79.4)	27 (36.5)	
No details	-	-	

** p value from χ_2 tests, Fisher's tests, t test, Wilcoxon test.*

"frequent" (e.g. everyday use and more than 3 times a week) and "sporadic" (meaning that the subject tried cannabis only once or twice lifetime, a few times each month and a few times each year). Cases who were cannabis consumers were more likely to smoke more frequently than controls (adj. OR = 4.4, 95% CI 1.08-18). Frequency of cannabis use was further analysed in terms of "daily use" as opposite to "less than daily use". Consistently with a previous study in an UK sample of FEP [3], in our sample cases were 7.5 times more likely to smoke cannabis everyday compared to controls ($\chi 2$ = 9.4, df = 1, p-value = 0.004; adj. OR = 7.5, 95% CI 1.9-29.7).

Moreover, we compared the total number of times that cases and controls had smoked cannabis lifetime ("up to 50 times" *versus* "between 50 and over 200 times") and we found that patients were more likely than controls to have used cannabis between 50 and over 200 times (adj. OR = 5.0, 95% CI 1.5-16.4).

We did not find a difference in duration of use of cannabis use between cases and controls. Mean duration of cannabis consumption was 7.4 years for cases and 6.8 years for controls (Welch test t = -0.3, df = 45, p = 0.785).

Table II. Patterns of cannabis use in cases and controls.

	Cases (n = 68)	Controls (n = 74)	p*
Cannabis use lifetime, n (%)			
Yes	29 (44.6)	42 (56.76)	0.153
No	36 (55.4)	32 (43.2)	
No details	3	0	
Current cannabis use* (at the time of the assessment), n (%)			
Yes	14 (51.85)	9 (21.4)	**0.009**
No†	13 (48.15)	33 (78.5)	
No details	2	0	
Frequency of cannabis use, n (%)			**0.003**
Everyday	12 (44.4)	4 (10.8)	
Less than everyday	15 (55.5)	33 (89.2)	
No details	2	5	
Total number of time used, n (%)			**0.011**
< 50 times	7 (27)	22 (59.46)	
> 50 and over 200	19 (73)	15 (40.54)	
No details	3	5	
Age of first use, mean (sd)	16 (2.34)	19 (5.37)	**0.002**
Mean duration cannabis, years, (sd)	7.4 (7)	6.8 (7.67)	**0.670**

**p value from χ_2 tests, Fisher's tests, t test, Wilcoxon test. †No current use was defined as no cannabis consumption in the previous 4 weeks as reported in the GAP study. The first row refers to all the sample of cases and controls while the following rows of the tables refer only to the subgroup of cannabis smokers in cases (n = 29) and controls (n = 42).*

Discussion

We found that in the Palermo sample lifetime cannabis exposure was similar in patients and in healthy controls. However, lifetime cannabis use does not say much about the extent of exposure to cannabis, since it is likely that some people only tried cannabis a few times in their life. A more significant index of cannabis exposure is cannabis consumption before the onset of psychosis; in this work we considered "cannabis consumption at the time of assessment". Cases were 5 times more likely than controls to be current users at the time of assessment, and this suggests that patients may have smoked more recently than healthy controls but it does not really give any information on the degree of cannabis exposure. As reported in the literature, there is a dose-response relationship between cannabis consumption and risk of psychotic disorder [2]. Frequency is one of the parameters of cannabis consumption that can modulate the risk for psychosis [26]. In the Palermo sample, cases who smoked cannabis were four time more likely to be frequent users than controls, who tended to use cannabis in more a sporadic way. Furthermore, in line with the GAP study findings [3], cases were 7.5 times more likely to smoke cannabis everyday compared to controls. While these results confirm the role of frequency of cannabis use in increasing the risk of developing psychotic disorder, they prevent any firm conclusions about direction of causality. However, a meta-analysis of prospective studies demonstrated that the effect of cannabis use on psychosis was not fully accounted by prodromal psychotic symptoms that may had driven cannabis use, and did not simply reflect the acute psychotogenic effect of cannabis [10]. Arsenault et al. reported an association between earlier age at first cannabis use and a higher risk of schizophrenia [9]. In Palermo sample, cases started smoking cannabis significantly earlier than controls; in fact, cases were more likely than healthy controls to have started cannabis consumption before the age of 15 years. This is interesting because some authors suggested that cannabis consumption may impact on brain development, and that early adolescence may, therefore, be a critical period for effects that do not occur when exposure begins later [27].

These results confirm the different pattern of cannabis consumption in people affected by psychosis and this may lead to consider cannabis as a contributing factor in the aetiology of psychotic disorders.

We controlled for the role of possible confounders as socio-demographic (age, gender, level of education and employment) and other environmental risk factors (other drug use and stimulant use). Demonstrating that frequency of use and early cannabis consumption is associated to an increased risk of psychosis may have relevance in public health prevention strategies and in organizing specific educational programs for adolescents.

This study has some limitations. Only one third of the FEP cases identified in the incidence part of the study were recruited in the case control analyses, but reassuringly there were not significant differences in terms of gender, ethnicity migration, level of education between participants and non-participants. For the selection of controls, an effort has been made to get a representative sample of the general population and controls were similar on a number of socio-demographic factors (age, gender, migrant status, level of education) to the population the cases come from. We do not think that selection bias might have influenced the results. A further source of bias is recall bias, because the information on the exposure was collected after the disease onset. However, it is unlikely that cannabis consumption was under-reported in our sample; in fact, lifetime cannabis consumption – both in cases (44%) and controls (56.7%) – was higher than in the Italian general population (22%). Furthermore, previous studies explored the impact of cannabis potency on psychosis risk [3], in our sample however, we did not have the chance to measure the effect of low and high potency kinds of cannabis due to the low exposure in Palermo to high potency cannabis (only 3 cases and 4 controls had ever tried high potency cannabis).

Conclusions

In the present study patients were more likely than healthy controls to have started to smoke cannabis before 15 years, and to have a higher frequency of use. Our data support an association between cannabis exposure and especially of everyday cannabis consumption and the risk of psychosis; however we are aware that the retrospective study design does not allow drawing definite conclusions about direction of causality.

Take home messages for psychiatric care

- Frequent cannabis use may increase the risk of developing psychosis
- Smoking cannabis in early adolescence may lead to psychosis

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