Original Article

Risk factors associated with the age onset of the first psychosis episode in schizophrenia of Moroccan patients: retrospective study on the role of the prodromal signs, family psychosis, and cannabis.

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ABSTRACT

Background

Prodromal signs are a valuable factor, but they can be challenging to serve as predictive indicators in schizophrenia; meanwhile, other significant risk factors, like family history and cannabis use, are well-documented high-risk factors.

Aim

This present study aimed to examine the association between the age at onset of psychosis and prodromal signs, family history of psychosis, and cannabis use independently, as well as the impact of their interaction.

Methods

Our study employed a retrospective approach and recruited 200 Moroccan patients clinically diagnosed with schizophrenia with a mean age of 31.47 years (± 8.39) from the Ar-razi Psychiatric Center of ibn Sina Hospital. Clinical data were collected in the presence of a qualified psychiatrist via a structured questionnaire.

Results

we found that the more prodromal signs a patient had, the age at onset of psychosis was slightly lowered with a non-significant small effect [E= -0.04; CI(-0.69) – (0.61); p= 0.89], similarly effect was observed to the presence of family psychosis [E= -0.12; CI(-1.79) – (1.53); p= 0.87], however the cannabis users patients showed a statistically significant association with an earlier age at onset of psychosis by lowering it 2 years compared to non-cannabis users [E= -2.23; CI(-4.28) – (-0.18); p= 0.03], their interaction had also a small effect at the age at onset of psychosis by the presence of prodromal signs.

Conclusion

cannabis use was associated with an early age at onset of psychosis, and this trend was consistent among patients who exhibited more prodromal signs. Even though other risk factors were non-significant, they also had a small effect influenced by the presence of prodromal signs.

Keywords

Prodromal signs; cannabis; family psychosis; schizophrenia; Age at onset.

INTRODUCTION

Schizophrenia is a complex psychiatric disorder that necessitates a multifaceted pharmacological intervention and various therapeutic interventions for better management and treatment; its prevalence in the global population is estimated to be around 1% [1] , it is crucial to note that the prognosis of schizophrenia has been documented to show significant difficulties in light of its ambiguous etiology and the varied spectrum of its clinical manifestations, particularly in the evaluation of the first episode of psychosis[2]**.** The first episode of psychosis frequently manifests symptoms that overlap with those observed in other psychiatric conditions, including schizoaffective disorder, bipolar disorder, and major depressive disorder featuring psychotic symptoms; this symptom overlap makes the process of differential diagnosis particularly challenging [3,4]. The prodromal phase often referred as "High-risk state" is an interval of time that precedes the first episode of the pathology, the phase is characterized by the sight of early nonspecific symptoms, which

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affect personal and social areas of the individual's functioning and can last for an undetermined period; Symptoms during this prodromal phase frequently include behavioral irregularities, mood fluctuations, and cognitive alterations, such as increased irritability, emotional instability, restlessness, and modifications in social interactions, including tendencies towards withdrawal or social isolation.[5,6]. The identification of the prodromal symptoms is often retrospective, relying on patients' and family reports, which can be influenced by memory biases and inaccuracies [7,8]; As reported in previous research on the prodromal period, while the prodromal signs can precede the first psychosis episode, they do not predict the onset, making it difficult to anticipate the onset of schizophrenia accurately[9]. Indeed, various individuals with the symptoms did not develop psychosis, emphasizing the need for more research[10]. Therefore, in the latest version of DSM-5, the prodromal signs are included in the category of "attenuated psychotic syndrome"(APS), along with other conditions for further study, reflecting ongoing interest in early detection for psychosis[11].

Although the risk factors of schizophrenia are multiple and remain to be clarified, over the past decade, research has shown that the interaction between genes and environmental factors represents high-risk factors; even though little is known about how these genetic and environmental factors interact to cause schizophrenia, previous studies have proved their implication. [12] Studies of twins reported that the heritability of the illness was evaluated at 80% approximately. [(13–15).] First-degree relatives of individuals with schizophrenia have a 10–15-times greater risk, and if both parents are schizophrenic, the risk of the offspring could increase to 35–45% [(16)]. And after decades of research, specific genetic alleles have been reported to be associated with schizophrenia, collectively explaining a minor fraction of their implication in schizophrenia; the latest update suggests that the SNP (Sing` heritability makes the biggest contribution, with an estimated heritability of 25% [17], then RCVs (Rare coding variants) were estimated to have a burden heritability of around 2% [(18)]. These studies show that family history is among the most significant risk factors, which could significantly enhance the likelihood of conversion to psychosis. [(19,20)].

Several social environmental factors associated with an increased risk for schizophrenia have also been identified, including cannabis abuse. In the general population, cannabis is the most used drug after tobacco. Its legalization for medical use has decreased the harmfulness of cannabis in the perception of the population [21], consequently increasing its consumption despite the well-known fact that cannabis abuse can cause psychotic-like experiences [22,23], and psychosis is one of the principal traits in the schizophrenia spectrum symptoms[1]. The first evidence that cannabis may be a causal risk factor for later schizophrenia was provided by Andreasson and colleagues, followed by several studies that agreed with the hypothesis of the association of cannabis use and the risks of psychosis in vulnerable individuals in general, and psychotic symptoms in schizophrenia [(24–27)]. In Morocco, a recent study reported that out of 95 schizophrenic patients, 69 had a history of cannabis use, which represents approximately 72.6% of the sample [28].

Overall, existing studies on the age onset of the first episode in psychiatric pathology are limited, particularly in the African continent; knowing the high stigmatization of mental illnesses like schizophrenia on the continent, more studies on risk factors are highly needed for a sense of awareness on early intervention and detection before the onset of the pathology. In this present study, we aim to investigate the association between the age onset of the first psychosis episode and risk factors, including prodromal count, family history of psychosis, and cannabis use, in a North African (Moroccan) cohort diagnosed with schizophrenia.

METHODS

Patients

This study used a retrospective design with a cross-sectional approach over two years (2020-2023). We recruited 200 patients clinically diagnosed with schizophrenia according to the DSM-5 (APA,2013), including 180 men and 20 women, hospitalized in the psychiatric ward of the Ar-Razi Hospital, Sale, Rabat, in Morocco, with a mean age of 31.47 years (± 8.39). A qualified psychiatrist evaluated the capacity of each patient to provide informed consent, ensuring confidentiality. All data were gathered in the presence of their respective psychiatrists through a structured questionnaire, and patients with other neurological and/or psychological conditions were systematically excluded from the study. The study obtained the validation of the ethics Committee of the Faculty of Medicine and Pharmacy in Rabat, the ethics approval

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Variables

The structured interview of the patients provided a total of four distinct prodromal symptoms, such as decline in functioning, disorganized speech, emotional withdrawal, and social withdrawal; their relative significance was assessed by presence or absence. To capture the overall burden of these symptoms, we summed the presence of prodromal symptoms for each patient, which gives a new variable termed "Prodromal count" ranging from 0 (all prodromal signs are absent) to 4 (all of the prodromal signs are present). The family history of psychosis was recorded as either "yes", "no", or "no data", the use of cannabis was recorded as "yes" or "no"; and finally, the age at onset of the first psychosis episode was recorded as a continuous variable, referring to the age which each patient manifested for the first time an identifiable psychosis episode.

Statistical analyses

A descriptive analysis was performed to distinguish the distribution of sociodemographic and clinical variables among the patients. We performed a linear regression model to investigate the association between the age of onset, which was set as a dependent variable, and the risk factors as predictors, which include prodromal signs, family history, and cannabis use. The fitted linear regression model procured a predicted value of age at onset evaluated with a confidence interval of 95%, across the range of prodromal count, stratified by the interaction of family history and cannabis use. The open-source program, R version 4.4.1, was used for all the above statistical analyses [29], and the results were considered significant when $p<0.05$.

RESULTS

Our analysis reveals in Table 1 the statistical description for all variables; the majority of patients were males, about 90%, and females represented just 10% of the patients. The patients were predominantly single (90.5%), descendants of Arab ethnicity (88.5%), and almost half of the patients had not completed a secondary education (49%), with a mean age of 31.47 years, with a standard deviation of ± 8.39 years. the mean age at onset of the first psychosis episode was 22.23 (±5.09) years. Among the four distinct prodromal signs, emotional withdrawal (52.5%) and social withdrawal (50.5%) were the predominant characteristics, present in almost half of the patients, followed by the decline in functioning (38.5%) and the disorganized speech (30.5%). Patients who had one of the previously cited prodromal signs represented 32%, followed by those who had two (29%), and those with three (12%) or four (11.5%) prodromal signs had nearly the same percentage. Patients with close relatives who have suffered from a psychological illness were less (36%) compared to those without a family history of psychosis (47%), and 17% of the patients and guardians did not know about their family history. The use of cannabis was widely common among the patients; 162 out of 200 patients consumed cannabis.

The association between the age at onset of psychosis and risk factors, which includes prodromal count, family history of psychosis, and cannabis use, is shown in Table 2. Our findings revealed that for each additional unit of prodromal signs in the prodromal count, the age at onset of psychosis is estimated to be lower by 0.04 years compared to when the patient had any prodromal signs; however, the confidence interval is wide, including 0 [(-0.69) – (0.61)], with a non-significantly small effect ($p = 0.89$). For patients with a family history of psychosis, the average age at onset decreased by 0.12 years compared to patients without a family history of psychosis; the effect was not significant ($p = 0.87$), and the confidence interval included both values, negative and positive [(-1.79) – (1.53)]. The patient with a positive consumption of cannabis had an earlier age at onset compared to the patient without; unlike other risk factors, the positive use of cannabis in patients and the age at onset of schizophrenia within our cohort was statistically significant as the p-value was below 0.05 ($p = 0.03$), the regression showed that the use cannabis of cannabis lowered the age at onset of the psychosis by 2.23 years, with a consistent effect as the 95% confidence interval is below 0 [(-4.28) – (-0.18)].

The predicted age at onset was calculated from a fitted linear regression analysis with a 95% confidence interval, providing the effect on how age at onset varies with prodromal count by interaction with family history of psychosis and cannabis use in Figure 1. We could observe that in the presence of more prodromal signs, the difference in age at onset between having or not having a family history of psychosis was not highly distinct. Also, patients with a family psychosis history of psychosis, who also consumed cannabis, had an earlier age at onset of psychosis compared to the

patients without any family history of psychosis and no consumption of cannabis, and the trend was lower when patients had more prodromal signs (predicted ages at onset for each interaction with confidence intervals were detailed in supplementary materials).

Table 1: Descriptive profile of Sociodemographic and clinical variables of patients.

Variables	Category	Effective	Percentage	Mean (±SD)
Sex	Males	180	(90%)	-
	females	20	(10%)	-
Marital status	Single	181	(90.5%)	-
	Married	19	(9.5%)	-
Ethnicity	Arab	177	(88.5%)	-
	Amazigh	23	(11.5%)	-
Education	University	39	(19.5%)	-
	Secondary	63	(31.5%)	-
	< Secondary	98	(49%)	-
Actual age	year	-		31.47 (± 8.39)
Age onset of Psychosis	year	-		22.23 (±5.09)
Prodromal signs	Decline in functioning	77	(38.5%)	-
	Disorganized speech	61	(30.5%)	-
	Emotional withdrawal	105	(52.5%)	-
	Social withdrawal	101	(50.5%)	-
Prodromal count	0	31	(15.5%)	-
	1	64	(32%)	-
	2	58	(29%)	-
	3	24	(12%)	-
	4	23	(11.5%)	-
Family history of psychosis	Yes	72	(36%)	-
	No	94	(47%)	-
	No data	34	(17%)	-
Cannabis users	Yes	162	(81%)	-
	No	38	(19%)	-

(N): Effective; (SD): Standard Deviation.

Table 2. Association of risk factors with the age at onset of schizophrenia by multinomial logistic regression analysis.

Risk factors	Estimate	Std.error	Statistic	p.value	Conf.low	Conf.high
Prodromal count	-0.042	0.332	-0.127	0.899	-0.698	0.614
Family history of psychosis (yes)	-0.129	0.844	-0.153	0.879	-1.796	1.537
cannabis use (yes)	-2.231	1.038	-2.150	0.033**	-4.281	-0.182

(**): Significant; (Std.error): Standard error; (Conf): Confidence interval

(colored ribbons): Confidence interval 95% of age at first episode

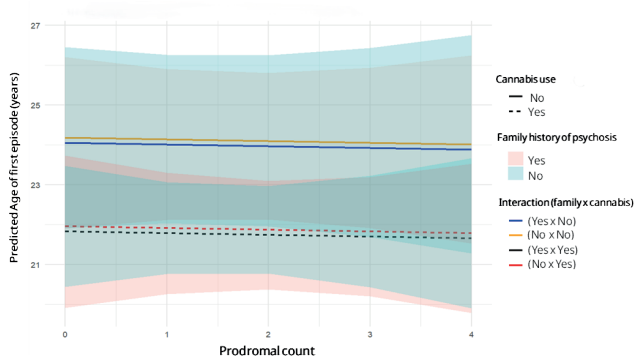

Figure 1. Adjusted predicted age of first episode of psychosis by prodromal count, interaction of family history of psychosis and cannabis use, with 95% confidence intervals.

DISCUSSION

The sociodemographic distribution results had shown disparity; the majority were males, single, and without a higher education. Our results align with a previous study that reported out of 7,628 Chinese schizophrenic patients, fewer were females, and the majority were single with a lower education [30,31]. Previous studies conducted in Morocco also support our result, showing a predominance of males among schizophrenia patients in Taza province[32] with a higher prevalence of single patients [33] and a lower level of education [34]. The mean age of our patients was 31.47 (± 8.39) years, while the

mean age at onset of psychosis was 22.23 (±5.09) years.

Based on our findings, the repartition of the schizophrenia prodrome identified within our patients shows that emotional withdrawal (52.5%) and social withdrawal (50.5%) were the most common signs, followed by the decline in functioning and disorganized speech, which were the least common among the schizophrenia patients. This finding is consistent with previous research, which reported that 52,5% of the patients presented negative symptoms like emotional withdrawal before their admission [5] Social withdrawal was a significantly prominent symptom in the schizophrenia prodrome, especially in the early detected subgroup, with approximately 26% of the sample, and the subgroup with more pronounced mixed prodromal signs, which comprises 46% of the participants[35]; indicating that social withdrawal is a critical characteristic in the development and progression of psychosis that can influence both physical and psychological health, it is related to the deficits in object relations and reality testing, which contribute to the social dysfunction experienced by individuals with mental disorders [36,37] . The decline in functioning (38.5%) and disorganized speech (30.5%) were modestly present in this study, as reported in a meta-analysis, the decline in functioning is a very subtle early symptom, typically manifested as cognitive impairment, such as intelligence, working memory, social performance, and executive functions [38] and disorganized symptoms, such as speech, are also a critical prodromal sign, even though it is not frequent; previous research reported that individuals at clinical high risk of psychosis often exhibited disorganized speech, which could predict the declines in social functioning [36] and the transition to psychosis, researchers identified minor syntactic and semantic abnormalities, such as poverty of speech, higher usage of possessive pronouns, and poor semantic coherence; using automated speech analysis tools, they identified that in 79% of the cases, these signs were predictive of psychotic transition [39]. Overall, it is essential to recognize the contextual nature of prodromal symptoms, as individual experiences and perspectives can vary among patients. Further research is needed to explore the long-term impact of interventions and the role of social processes in the onset of psychosis episodes and the progression of mental illness. The majority of patients in this study were cannabis users, which aligns with a previous study indicating that daily users of cannabis had rates of psychotic symptoms that were between 1.6 and 1.8 times higher than in nonusers of cannabis; at the population level, the incidence of schizophrenia decreased by approximately 8%, supposing a causal association when the consumption of cannabis was removed [25,40] and the incidence of not specified psychosis increased from 30.0 to 55.1 per 100,000 individuals (83.7%) in the post-legalization period relative to the pre-legalization period of medical use of cannabis [41].

Family history of psychosis is well documented as a considerably higher risk factor for schizophrenia [42] in a Danish study, the relative risk of schizophrenia was reported to be higher for individuals with a family history of schizophrenia, even though the risk factor is not determinative; people with first-degree relatives affected, like persons with a mother (9.31, 95% CI[7.24-11.96]), father (7.24, 95% CI[5.10-10.16]), or sibling (6.99, 95% CI[5.38-9.09]), were at higher risk of schizophrenia compared with persons with no affected parents or siblings [43], we found in this study that only 36% of patients had a family history of psychosis; however, there was no significant association with the age at onset of psychosis.

This present study investigated the relation between the age at onset of psychosis and prodromal count, family history of psychosis, and cannabis consumption. We found that each of these predictors had an effect on the age at onset of schizophrenia; however, only the positive consumption of cannabis was significant, with an elevated effect on age at onset. For an additional point in prodromal count, the age at onset of psychosis decreased by 0.04 years, but not significantly; a similar effect was also observed in patients with a family history of psychosis, the average age at onset was lower by 0.12 years, which is slightly higher than prodromal count but still not significant. Our findings are consistent with a previous study, which divided patients into 2 groups: one as an early onset of psychosis group (15.5 ± 1.8 years), and one as an adult onset of psychosis group (25.2 ± 5.1 years), the result showed that the early-onset group had more prodromal signs than the adult-onset psychosis group [44]. In contrast to the late deduction, Pietro Carmellini and colleagues did not find a difference in median age of onset between those who had childhood prodromal symptoms vs those who did not, revealing that more prodromal signs in childhood were not clearly associated with a significantly earlier onset in their study [45]. A meta-analysis performed in 15 studies

showed that family history of psychosis has a small but significant impact on age-at-onset [46]. Moreover, our study revealed that patients with a positive consumption of cannabis had an statistically significant earlier age at onset of psychosis compared to the patients without, by a reduction of approximately 2 years; this finding is concordant with a large meta-analysis including 83 studies, which reported the age at onset of psychosis for cannabis users was to be earlier by 2.70 years younger (standardized mean difference = -0.414) than for non-cannabis users [47,48]. The interaction between the family history of psychosis and cannabis use by the prodromal count was used to predict the variation of the age at onset of psychosis. Prodromal symptoms, *per se,* are challenging with no reliable predictive value; however, associated with other factors, they give valuable insight. We observed that patients with a positive family history of psychosis and cannabis use had a slightly lower age at onset of psychosis when all four prodromal symptoms were present, compared to when prodromal symptoms were absent. In addition, the family history of psychosis showed clearly that as the prodromal count increases, the gap of age at onset becomes narrower between the patients who have a family history of psychosis and those who do not. This result indicates the crucial participation of the prodromal symptoms in the manifestation of the illness[49].

Various limitations in this study impose careful interpretation. First, the majority of patients in our research were men and in a single site, which suppresses the applicability of our findings to a larger population. Secondly, this research was conducted with a relatively limited cohort, due to numerous challenges encountered in recruiting patients diagnosed with schizophrenia, which stems from their elevated vulnerability and related clinical conditions. The lack of availability of some data in family history and the age at onset of the prodromal phase limited further detailed interactions between risk factors[50].

CONCLUSION

This present study revealed that among our patients, there was a statistically significant association between cannabis use and the age at onset of psychosis; other risk factors like family prodromal count and psychosis had a small effect on age at onset of psychosis, but this effect was not statistically significant. Additionally, the interaction between family psychosis and cannabis use slightly lowered the age at onset of psychosis when stratified by prodromal count. This reminds us of the importance of early intervention before the transition to psychosis, research on prodromal signs and their interaction with others risk factors in schizophrenia would be beneficial for personalized treatment approaches through collaborative studies especially in Africa, involving multiple countries to encompass a broader range of ethnicity and cultures, which could identify subgroups of patients who may benefit from specific early intervention strategies and could contribute to the machine learning process for effective personalized intervention and treatment.

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Data statement: All data are available with a reasonable request to the author, due to the ethical condition to ensure confidentiality of the patients' data.

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