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Association between Paraoxonase 1 (PON1) and Suicidal Risk in Patients with Schizophrenia

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Abstract

Background: There have been many studies on psychiatric disorders, but very little is known about the biology of suicide with schizophrenia. In the present study, we are looking for a possible connection between paraoxonase 1 (PON1) and suicidal behavior in schizophrenic Tunisian patients.

Methods: Assay of PON1 has been done for 170 schizophrenic patients with and without suicide attempts and 119 healthy controls. All patients enrolled in the study were evaluated by psychometric scales (PANSS, EGF, CGI, BPRS and CALGARY).

Results: In our study, a significant decrease in the enzymatic activity of PON1 was found in schizophrenia patients compared to controls. PON1 was also significantly lower in schizophrenic patients with suicide attempt compared to those without suicide attempt. In our work, a weak correlation between the psychometric scale CGI severity of the disease, PON1 activity and suicidal act was found.

Conclusions: Results of this study showed that PON 1 levels in schizophrenic patients after suicide attempt was significantly lower than in patients with suicide attempt. PON1 may be one of the biological markers of susceptibility to suicide in patients with schizophrenia.

Keywords: Paraoxonase1; Schizophrenia; Suicide

Introduction

Suicide is a complex phenomenon that has long attracted research interest. This is a serious universal public health problem and affects all age groups and both genders. In 2012, the World Health Organization (WHO) estimated that one million people died every year by suicide. Given its social impact and its impact in terms of cost, suicide requires the implementation of an action plan allowing for upstream intervention and care for those at risk.

In Tunisia, especially after the revolution, the number of suicides continues to increase. The Social Observatory under the Tunisian Forum for Economic and Social Rights [1] announced that the number of suicides registered in 2015 reached 549 cases of successful suicides and suicide attempts throughout the republic with an increase in order of 170.4% compared to 2014. Studies on the theme of suicide and suicide attempts in Tunisia remain rare, the first published work dates from thirty years.

Subjects who commit suicide do not always clearly express their intentions before taking action, which makes the predictability of suicidal behavior very uncertain, and it is difficult to establish a precise profile of the suicidal subject.

Several studies [1-4] were designed to identify factors of suicidal risk. Among the main risk factors is the presence of an identifiable mental health disorder such as mood disorders and schizophrenia [1-4]. In addition to mental pathologies, some biological perturbations are strongly associated with suicidal behavior [5,6]. Moreover, oxidative stress is implicated in the pathophysiology of certain mental diseases, including schizophrenia [7,8].

According to the results of studies using the psychological autopsy method, more than 90% of suicides are affected by one or more psychiatric disorders at the time of the suicidal act [9].

Many studies show a strong association between schizophrenia, one of the most severe mental disorders, and suicidal behaviors. Indeed, suicide is the leading cause of death for individuals with schizophrenia [10,11]. The prevalence of suicide deaths in this group is estimated at 6-15% [10]. However, a meta-analysis by Palmer et al. [10] estimates the prevalence of suicide deaths among people with schizophrenia at 4.9% and confirms that a significant proportion of deaths occur more particularly around an acute episode of the disease. Although 50-80% of attempted suicides have no fatal outcomes, a history of attempted suicide is common among schizophrenics who die by suicide. Lifetime prevalence rates are estimated to be between 40% and 50% [12,13]. In addition, 10-15% re-offends and dies, while 11% die within the first year after diagnosis [13,14].

Among the biological markers that could be involved in the suicidal process is paraoxonase 1 (PON1), an enzyme belonging to the group. An esterase family such as cholinesterases or carboxylesterases that have the ability to hydrolyze organophosphorus compounds [15].

Some authors have reported that PON1 activity is lowered in schizophrenia and that this decrease is related to oxidative stress [16,17].

Our work aims to study the variations in the activity of PON1 as a potential marker of vulnerability to suicide in patients with schizophrenia.

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Methods

170 schizophrenic patients (78 of them with suicide attempt) were recruited during 11 months (April 2013 – March 2014) at the department of psychiatry and 119 control subjects were recruited from the blood bank in the University Hospital of Monastir, which is located in the Mid-eastern part of Tunisia. All subjects are free of any psychiatric or metabolic pathology. All patients met DSM-IV diagnostic criteria. Our work was approved by the ethics committee and all patients participated voluntarily. Before participating in this study, a consent form was signed by the participant or by his / her legal guardian. Patients were recruited during hospitalization in the psychiatric department or during specific consultations for schizophrenia. All patients enrolled in the study were evaluated by the following psychometric scales:

PANSS (Positive and Negative Syndrome Scale)

Evaluation of positive, negative symptoms and general psychopathology.

CGI (Clinical Global Impression)

Evaluation of the severity, therapeutic index and improvement of the patient's condition under treatment.

EGF (Global Functioning Assessment Scale)

Assessment of psychological, social and occupational functioning on a hypothetical continuum ranging from mental health to disease.

BPRS (Brief Psychiatric Rating Scale)

Abbreviated scale of psychiatric appreciation.

CALGARY

Depression scale for schizophrenia.

For each subject, 5 mL of blood were taken from a tube containing lithium heparinate. The determination of the biochemical parAmelters studied was carried out by colourimetric enzymatic methods on COBAS 6000™ (Roche Diagnostic). The LDLc was calculated using the Friedwald formula. The activity of paraoxonase1 (PON1) was determined by a kinetic method using paraoxon as substrate on Konelab™30 (Thermo Electron Corporation).

Data analysis was performed using SPSS® software version 21.0 (Statistical Package for Social Sciences). The results were expressed as mean ± SD for the Gaussian distribution variables. For the analysis and comparison of qualitative and quantitative variables, we used the $\chi 2$ test, the Student test, the Anova analysis and the Roc curve. The difference was considered significant when $p \leq 0.05$.

Results

Tables 1 and 2 shows the anthropometric and lifestyle characteristics of the study population, subjects with schizophrenia and control subjects (Table 1) and schizophrenia subjects with and without history of attempted suicide (Table 2). All parAmelters studied (age, gender, BMI, smoking status and alcohol status) for the two schizophrenic and control groups are confounding factors ($p<0.25$), and only age and alcoholic status are confounding factors for our patients (with and without history of attempted suicide).

By comparing the mean plasma concentrations of biochemical parAmelters that may influence paraoxonase1 (PON1) activity in patients with schizophrenia without history of attempted suicide (SI) versus those with a history of suicidality, we noted that four parAmelters (uric acid, ASAT, total cholesterol and HDL-c) are confounding factors ($p<0.25$) and that total cholesterol is significantly lower in suicidal subjects compared with those without suicide attempt ($p<0.001$) (Table 3).

ParAmeltrs	Schizophrenia (n=170)	Healthy controls (n=119)	p
Age (years)	40.32 ± 11.94	41.41 ± 10.03	0.209
Gender (M/F)	127/43	64/55	**<0.001**
BMI (kg/m²)	25.82 ± 5.53	23.52 ± 3.44	**<0.001**
Smooking	96	36	**<0.001**
Alcohol	53	9	**<0.001**

Table 1: Anthropometric characteristics and life hygiene for different groups of study.

ParAmeltrs	Schizophrenia (n=170)		
	Patients without S.A.(n=92)	Patients with S.A.(n=78)	p
Age (years)	39.67 ± 11.97	39.77 ± 12.20	0.958
Gender (M/F)	73/19	52/26	0.038
BMI (kg/m²)	25.38 ± 5.70	26.23 ± 5.19	0.317
Smooking	55	44	0.744
Alcohol	25	28	0.166

Table 2: Anthropometric characteristics and life hygiene of patients.

Table 4 shows that the mean activity of PON1 was significantly lower in patients compared to controls ($p<0.001$) before and after confounding factor adjustments (Age, gender, BMI, alcoholic status and smoking status).

We noted a significantly lower mean PON1 activity in suicidal patients compared to the others ($p<0.001$) (Table 5).

Comparison of the clinical and therapeutic characteristics of patients with schizophrenia according to the presence or absence of a history of S.A. showed no significant difference between these two groups (Table 6).

We also found no significant differences in the type of schizophrenia, but the majority of these patients with a history of S.A. were paranoid while the majority of patients without SA were disorganized.

The study of the correlation between mean paraoxonase activity and psychometric evaluation scores in patients with schizophrenia with and without S.A. showed a positive correlation between the absence of suicidal history and scores CGI disease severity and CGI therapeutic index (Table 7).

Using the comparative analysis of the ROC curve, the threshold value of the activity of PON1 retained for discrimination between suicidal and non-suicidal patients is 101.5 IU / L (Figure 1).

PON1 values below 101.5 IU/L were significantly associated with a suicidal risk four times higher than those above the threshold (Table 8).

The risk of suicidality in patients is multiplied by 6 for males compared to females ($p<0.001$), by seven for patients aged 25 to 35 years compared to others Slices of ages ($p=0.010$), by nine for the paranoid type of schizophrenia compared to other types ($p=0.002$), by eleven for patients using a combination of typical and atypical neuroleptics compared to those treated otherwise ($p=0.003$) (Table 9).

Discussion

The frequency of S.A. (45.88%) in our patients was higher than those reported by Harkavy-Friedman et al. [18], by Muller et al.

ParAmeltrs	Schizophrenia (n=170)		
	Patients without S.A.(n=92)	Patients with S.A.(n=78)	p
Age (years)	39.67 ± 11.97	39.77 ± 12.20	0.958
Gender (M/F)	73/19	52/26	0.038
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Smooking	55	44	0.744
Alcohol	25	28	0.166

Table 3: Mean plasma concentrations of the biochemical parAmelters studied according to the history of S.A. in our study population.

ParAmelters	Patients with schizophrenia (n=170)		
	Without S.A.(n=92)	**With S.A.**(n=78)	**P Value**
Uric acid (µmol/L)	253.66 ± 64.37	272.33 ± 61.48	0.065
Urea (mmol/L)	3.69 ± 1.33	3.62 ± 1.08	0.708
Bilirubin (µmol/L)	695 ± 13.51	5.77 ± 3.81	0.466
Albumin (g/L)	42.3 ± 7.00	43.55 ± 4.80	0.319
Proteins (g/L)	68.55 ± 16.00	67.27 ± 7.99	0.534
ALAT (UI/L)	12.79 ± 19.00	11.90 ± 8.67	0.710
ASAT (UI/L)	19.50 ± 11.91	24.73 ± 25.65	0.094
Gamma GT (UI/L)	22.98 ± 15.36	22.14 ± 15.91	0.736
ALP (UI/L)	69.59 ± 22.06	69.78 ± 19.54	0.954
Total Cholesterol (mmol/L)	4.41 ± 1.05	3.83 ±1.24	**0.002**
TG (mmol/L)	1.60 ± 0.94	1.48 ± 0.93	0.451
HDL-c (mmol/L)	4.30 ± 3.56	1.02 ±0.28	0.247
LDL-c (mmol/L)	3.01 ± 4.44	2.51 ± 0.95	0.360

Note: p[a]: p adjusted for age, gender, BMI, alcohol status and smoking status
Table 4: Comparison of mean PON1 activity between patients and controls.

ParAmelters	Patients with schizophrenia (n=170)			
	Without S.A. (n=92)	**With S.A.** (n=78)	**p**	**p**[a]
PON1 (UI/L)	256.77 ± 176.52	160.10 ± 128.96	**<0.001**	**<0.001**

Note: S.A.: Suicide attempt; **p**[a]: p adjusted for gender, alcoholic status, uric acid, ASAT, total cholesterol and HDL-c
Table 5: Comparison of PON1 activity in patients with and without suicide attempt.

[19] in Germany (36.7%), by Uzun et al. [20] in Turkey (34.7%) and Xiang et al. [21] in Beijing (33.6%). However, the frequency of S.A. in schizophrenia varies from 18 to 55% according to a meta-analysis by the team of Borges G et al. [22].

In our study, suicide attempts are characterized by a male predominance for patients with schizophrenia (73.52%). These results are consistent with those of Borges et al. [23]. In suicide studies, it is generally described that women commit suicide attempts much more frequently than men, whereas successful suicide is much more frequent in men [22].

We found that PON1 activity was significantly lower in patients with schizophrenia compared to control subjects before and after adjustment to confounding factors. PON1 activity was also significantly lower in suicidal than non-suicidal subjects. To our knowledge, very few studies have investigated the activity of paraoxonase in suicidal patients; Zhang et al. showed a decrease in PON1 activity in Chinese suicidal patients followed for psychiatric disorders. The sAmel team also found an association between exposure to pesticides, decreased activity of PON1 and the onset of suicidal ideation [24].

Several hypotheses have been demonstrated in this respect and several studies have shown that activation of inflammatory pathways as well as oxidative stress play an important role in schizophrenia. Low levels of antioxidants such as PON1 disrupt neuro-progressive processes (increased neuro-degeneration and apoptosis and decreased neurogenesis) that accompany schizophrenia [25-27]. The strong co-morbidity between certain psychiatric disorders such as schizophrenia and inflammatory diseases can be explained by lower antioxidant levels, including PON1 [14]. Some studies suggest an implication of PON1 in the regulation of cholesterol metabolism in macrophages. Rozenberg et al. reported that PON1 induces a decrease in the accumulation of cholesterol at the level of macrophages by the inhibition of its biosynthesis [27]. Rosenblat et al. showed that HDL-induced cholesterol efflux from transgenic mice over-expressing PON1 was greater than that provided by HDL from wild-type mice or invalidated mice for the gene of the PON1 [28].

In our study, the statistically significant decrease in the enzymatic activity of PON1 is more frequent in men than in women. This result is consistent with that of the study by Sumegová et al. explaining in part the lower incidence of atherosclerosis and cardiovascular disease in women. It is recognized that estrogens, especially oestradiol which is a phenol, can participate with other antioxidants in protection against atherosclerosis [29].

Several authors also suggest that smoking is an independent determinant of PON1 activity [30] and that the decreased activity of this enzyme is correlated with the number of cigarettes smoked per day and with the age of smoking [31]. The absence of significant variation in PON1 activity, as a function of smoking status, observed in our study may be attributed to some characteristics of smoking, nAmelly the age and number of cigarettes smoked per day, also knowing that the inhibitory effect exerted by the tobacco on the activity of the PON1 is reversible. A study by the Prakash et al. team confirmed the decrease in serum PON1 activity among alcohol users, suggesting that liver damage reduced its ability to produce the enzyme [32].

Neither the nature of the Neuroleptics administered nor the clinical form of schizophrenia was related to the history of attempted suicide in our patients. The results of previous studies [33,34] are divergent and according to Pompili et al. [35], it is more the evolution of the disease than its clinical form that predicts this complication. Indeed, the risk of suicide is related to the frequency of relapses, the severity of symptoms and the awareness of mental deterioration rather than to the clinical form of which the paranoid type is the most incriminated.

We also noted a decrease in PON1 activity as a function of treatment with a risk eleven times higher in patients treated with a combination of typical and atypical neuroleptics. Poor adherence to treatment in schizophrenia is widely accepted as a predictor of suicidal behavior. It would be the cause of the chronicity or even the aggravation of the psychotic symptoms, the increase in the number of relapses and therefore a pejorative evolution of the disease [36,37]. A study by the team of Gilca et al. showed that patients with schizophrenia and treated with atypical neuroleptics presented a decrease in serum PON1 activity [38]. The extrapyramidal effects of neuroleptics (Parkinsonism, akathisia, tardive dyskinesia) increase the risk of S.A. through the functional impairment they cause, by their own depressive effect and by the consequent alteration of the quality of life [39-41].

In our work, a weak correlation between the psychometric scale CGI severity of the disease, PON1 activity and the switch to suicidal act was found. Other authors report a positive association between suicidality

Types		Schizophrenia with S.A.(n=78)		Schizophrenia without S.A.(n=92)		p
		N (%)	PON1 (UI/L)	N (%)	PON1 (UI/L)	
Type of schizophrenia	Paranoid	31 (40.8%)	135.35 ± 91.11	28 (31.1%)	236.92 ± 179.24	0.181
	Undifferentiated	18 (23.7%)	159.38 ± 133.77	15 (16.7%)	234.66 ± 173.94	
	Disorganized	23 (30.3%)	207.82 ± 166.87	43 (47.8%)	271.79 ± 184.05	
	Other	4 (4.4%)	92.33 ± 68.13	4 (5.2%)	300.66 ± 178.80	
Neuroleptics	Typical	65 (83.3%)	167.41 ± 135.85	67 (73.6%)	260.20 ± 172.59	0.437
	Atypical	2 (2.6%)	144.00 ± 118.79	4 (4.4%)	186.75 ± 65.40	
	Typical + Atypical	8 (10.3%)	105.62 ± 68.32	12 (13.2%)	218.83 ± 158.65	
Longitudinal evolution	Episodic with residual symptoms between episodes	33 (42.9%)	180.03 ± 142.12	30 (33.3%)	228.76 ± 160.96	0.880
	Episodic without residual symptoms between episodes	3 (3.9%)	74.00 ± 49.11	12 (13.3%)	234.25 ± 165.60	
	Continue	35 (45.5%)	155.17 ± 126.37	34 (37.8%)	281.44 ± 210.04	
	Isolated in partial remission	6 (7.8%)	137.33 ± 68.31	10 (11.1%)	303.50 ± 144.54	
	Isolated in total remission	0 (0%)	161.27 ± 129.39	4 (4.4%)	160.75 ± 63.05	

Note: Other: Catatonic type or residual type; S.A.: Suicide attempt

Table 6: Study of the mean activity of PON1 according to the clinical and therapeutic characteristics of the patients.

ParAmelters	PON1 (UI/L)			
	With S.A.		Without S.A.	
	r	p	r	p
PANSS General	-0.170	0.146	-0.018	0.863
PANSS positif	0.015	0.895	-0.016	0.882
PANSS negatif	0.106	0.368	0.177	0.095
BPRS	-0.093	0.429	-0.036	0.736
CGI severity	-0.018	0.878	**0.214**	**0.042***
CGI therapeutic index	-0.046	0.697	0.120	0.259
CGI improving patients under treatment	-0.131	0.261	**0.227**	**0.031***
EGF	0.091	0.436	-0.060	0.575
Calgary	-0.155	0.185	-0.071	0.503

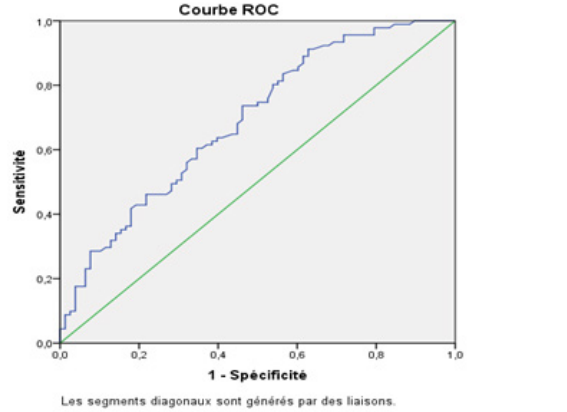
Note: S.A.: Suicide attempt

Table 7: Correlation between the scores of the psychometric evaluation and the activity of the PON1 for patients with and without S.A.

		Without S.A.	With S.A.	O.R.	I.C.	P
PON1 (UI/L)	**≤ 101.5 UI/L**	12 (13.2%)	48 (61.5%)	4.115	1.925-8.794	**<0.001**
	>101.5 UI/L	79 (86.8%)	30 (38.5%)			

Note: S.A.: Suicide attempt

Table 8: Study of the association between the activity of PON1 and suicidal risk in the study population.



AUC	p	Cut off value	Sensibility	Specificity
0.689	**<0.001**	101.5 UI/L	61.5%	86.8%

Figure 1: ROC curve of PON1 activity in patients.

and certain positive symptoms (delusions, loss of associations, theft of ideas, suspicion, etc.). According to Messias et al. there was neither a positive association nor a negative association.

Our study presents certain methodological limitations which should be taken into account when interpreting the results. The number of patients recruited is relatively low in each group studied and the study was carried out in a single university hospital, which makes the results not representative of all the Tunisian patients suffering from these types of psychiatric disorders would be at the origin of the lack Representativeness of the Tunisian population on the one hand and constitutes on the other hand a limit to the statistical power of the tests used.

Similarly, the absence of matching between patients and controls and between suicidal and non-suicidal patients required adjustments for age, gender, BMI, smoking status and alcohol status, Uric acid, ASAT, total cholesterol and HDL-c.

Conclusion

Types			Without S.A.	With S.A.	O.R	I.C.	p
Gender	**Male**	**≤ 129.5 UI/L**	25 (48.1%)	65 (87.8%)	6.687	2.762-16.191	<0.001
		>129.5 UI/L	27 (51.9%)	9 (12.2%)			
	Female	**≤ 129.5 UI/L**	14 (82.4%)	21 (80.8%)	1.111	0.228-5.411	0.612
		>129.5 UI/L	3 (17.6%)	5 (19.2%)			
Age	**<25 years**	**≤ 129.5 UI/L**	2 (18.2%)	3 (37.5%)	2.700	0.332-21.977	0.336
		>129.5 UI/L	9 (81.8%)	5 (62.5%)			
	25-35 years	**≤ 129.5 UI/L**	2 (9.1%)	10 (43.5%)	7.692	1.447-40.906	0.010
		>129.5 UI/L	20 (90.9%)	13 (56.5%)			
	>35 years	**≤ 129.5 UI/L**	8 (14%)	16 (34.8%)	3.267	1.247-8.554	0.012
		>129.5 UI/L	49 (86%)	30 (65.2%)			
Type of schizophrenia	Paranoid	**≤ 129.5 UI/L**	2 (7.1%)	26 (92.9%)	9.389	1.885-46.756	0.002
		>129.5 UI/L	13 (41.9%)	18 (58.1%)			
	Disorganized	**≤ 129.5 UI/L**	3 (20%)	6 (33.3%)	2.000	0.404-9.909	0.324
		>129.5 UI/L	12 (80%)	12 (66.7%)			
	Other	**≤ 129.5 UI/L**	7 (15.2%)	10 (37%)	3.277	1.868-8.610	0.034
		>129.5 UI/L	39 (84.4%)	17 (63%)			
Neuroleptics	Typical	**≤ 129.5 UI/L**	10 (14.9%)	24 (36.9%)	3.387	1.441-7.727	0.003
		>129.5 UI/L	57 (85.1%)	41 (63.1%)			
	Atypical	**≤ 129.5 UI/L**	0 (0%)	1 (50%)	2.000	0.500-7.997	0.333
		>129.5 UI/L	4 (100%)	1 (50%)			
	Typical + Atypical	**≤ 129.5 UI/L**	1 (8.3%)	4 (50%)	11.000	0.928-130.324	0.058
		>129.5 UI/L	11 (91.7%)	4 (50%)			

Table 9: Study of the association between PON1 activity, anthropometric (gender and age), clinical (type of schizophrenia) and therapeutic characteristics for patients <with and without S.A.

The activity of paraoxonase is lower in patients with schizophrenia compared to controls and is even lower in suicidal compared to those without suicide attempt. Paraoxonase 1 may be one of the biological markers of susceptibility to suicide in patients with schizophrenia. However, the mechanism by which this enzyme is involved in suicide in patients with schizophrenia remains unknown. To date paraoxonase remains an enzyme little studied since its substrate, paraoxon, is very toxic, moreover, since neither its natural substrate nor its function are not well known. As well as the factors influencing the activity of the PON1 in particular the genetic aspects must be taken into consideration.

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