Antipsychotics and Risk of Neuroleptic Malignant Syndrome Among a Sample of Egyptian Psychiatric Patients: Role of Alpha-synuclein as A Biomarker for Brain Damage

Muhammad E Musa[1], Abdel-Aziz Ghanem[1], Osama Shabka[1], Shimaa M Motawea[1] and Amal A El-Bakary[1]

KEYWORDS
Neuroleptic malignant syndrome,
Alpha-synuclein,
Antipsychotics,
Brain damage,
Auto-antibodies,
Human,
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ABSTRACT

Neuroleptic malignant syndrome (NMS) is a potentially fatal neurological emergency that occurs as an idiosyncratic reaction to antipsychotics. Human alpha-synuclein (α-syn) protein is a neuronal cytoskeleton-related protein that has been recently implicated in the development of chronic neurodegenerative disorders. This study was conducted to evaluate the correlation between serum levels of IgM and IgG anti-synuclein alpha (anti-SNCa) auto-antibodies and the risk of development of NMS in psychiatric patients administered antipsychotic medications, as well as to investigate the diagnostic value of these antibodies as potential biomarkers for diagnosis of antipsychotics-induced brain damage in psychiatric patients presenting with NMS. The study was carried out on 150 subjects, divided into three groups: group I (case group) included 30 psychiatric patients presenting with NMS, group II (positive control group) included 60 psychiatric patients on antipsychotic medications with no previous history of NMS, and group III (negative control group) included 60 normal healthy volunteers. Serum levels of IgM and IgG antibodies were measured using ELIZA. This study revealed that the median serum levels of both IgM and IgG anti-SNCa antibodies were significantly higher in the case group when compared with the two control groups ($p < 0.001$). Significant associations were identified between increasing serum levels of IgM and IgG anti-SNCa antibodies, chronic antipsychotic drug intake, and development of NMS among psychiatric patients, and that these antibodies can be used as predictor biomarkers for brain damage, with high sensitivity and specificity, in psychiatric patients presenting with NMS.

Introduction

Neuroleptic malignant syndrome (NMS) is an unpredictable acute idiosyncratic reaction to antipsychotics. It is characterized by a group of clinical manifestations, including changes in mental status, generalized muscular rigidity, hyperpyrexia, and disturbed autonomic functions. It can be lethal if not diagnosed and treated properly (Pileggi and Cook, 2016).

An immunologic hypothesis for NMS has been implicated, depending on the evidence that the acute-phase immunologic response is activated in this syndrome. Several mechanisms also have been postulated in the induction of this acute phase response, including autoantibody production, virus-drug interaction, heat stress, muscle breakdown, and psychological stress (Delgado et al., 2016).

In addition, patients with a history of NMS have been found to have autoantibodies against neurotransmitter receptors. The antigenic stimulus for induction of this immune response could be the antipsychotic medication itself, which interacts with endogenous proteins and neurotransmitter receptors in the brain, resulting in the initiation or even exacerbation of neuropsychiatric disorders, including NMS (Korchia et al., 2018).

Human alpha-synuclein (α-syn) protein is a neuronal cytoskeletal protein that has been closely associated with chronic neuro-

[1] *Forensic Medicine and Clinical Toxicology Department, Faculty of Medicine, Mansoura University, Egypt.*

degenerative brain disorders, such as Parkinson's disease (PD). Moreover, postmortem microscopic examinations of the brain tissues of patients with senile Lewy body dementia (LBD), a potential contributing factor for NMS, have revealed the presence of α-syn protein aggregates in the neurons of these individuals; a finding that could provide a suggested association between α-syn protein and acute emergency conditions as NMS (Goedert et al., 2017).

This work aims to evaluate the correlation between serum levels of the naturally occurring IgM and IgG anti-synuclein alpha (anti-SNCa) auto-antibodies and the risk of development of NMS in psychiatric patients administered antipsychotic medications, as well as to investigate the diagnostic value of these antibodies as potential biomarkers for diagnosis of antipsychotics-induced brain damage in psychiatric patients presenting with NMS.

Subjects and Methods:

Subjects:

The present study is a descriptive cross-sectional comparative case-control study that was carried out on 150 subjects, recruited from the Toxicology Unit of Mansoura University Emergency Hospital (MUEH) and Mansoura University Psychiatry Department, during the period from October 2018 to February 2020. They were divided into three groups: group I (case group), which included 30 psychiatric patients on antipsychotic medications presenting with NMS, group II (positive control group), which included 60 psychiatric patients on antipsychotic medications with no previous history of NMS, and group III (negative control group or healthy group) that included 60 healthy volunteers with no history of previous psychiatric troubles, receiving antipsychotic medications or having any of the neurodegenerative brain disorders.

This study was approved by the Institutional Review Board (IRB), Faculty of Medicine, Mansoura University (code: MD/17.12.50). All participants in the current study, or relatives of the confused patients in the case group, were fully informed about the goals of the research and the confidentiality of the results. From each participant, informed written consent was obtained, declaring his/her approval to provide history, undergo a clinical examination, and give a blood sample. Blood samples were collected from the NMS patients before intervention therapy.

Exclusion Criteria:

For all psychiatric patients who attended the Toxicology Unit, certain exclusion criteria were considered before enrolment. These criteria included the previous history of significant head trauma or traumatic brain injuries (Wang et al., 2016), neurosurgeries (Mondello et al., 2016), cerebrovascular stroke; either intracranial hemorrhage or ischaemic stroke (Glushakova, et al., 2016), epilepsy (Stanciu et al., 2019), meningitis or encephalitis (Rohlwink and Figaji, 2014), carbon monoxide toxicity (Akdemir et al., 2014), neurodegenerative brain disorders, such as PD (Shalash et al., 2017), AD (Zetterberg, 2019) and LBD (Koenig et al., 2018), brain tumor (Prinz and Priller, 2014), auto-immune disease and immune suppression therapy (El-Fawal, 2014), chronic alcoholism (Modi et al., 2016), addiction of any of the drugs of abuse, such as opiate and heroin (Cadet et al., 2014) and occupational exposure to pesticides for more than one year (Abd El Rahman et al., 2018).

Methods:

All participants were subjected to the following: (1) thorough history taking focusing on psychiatric disease duration and detailed profile regarding the prescribed

antipsychotic drugs within at least 2-4 weeks before NMS development, (2) full clinical examination together with available laboratory testing and radiological evaluation to assess for the classical clinical tetrad of NMS, as well as to exclude medical conditions that could mimic the syndrome.

From all participants, blood samples (5 ml from each subject) were drawn. Sera were stored in a deep freeze at -80°C until analysis. Measurement of the serum levels of IgM and IgG anti-SNCa auto-antibodies was finally performed using a microplate ELIZA reader (with a 450±10 nm filter), according to the manufacturer manual of the ELIZA kit purchased from American Research Products Inc. (Belmont, MA, USA; Catalogue No. AEB222Hu).

Statistical Analysis:

The collected data were coded, processed, and analyzed using Statistical Package for Social Sciences (SPSS) program for windows (version 22.0). One-way analysis of variance (ANOVA) test, Monte Carlo test, Chi-square test, Kruskal-Wallis, and Mann-Whitney U test were performed for statistical comparisons. Qualitative data were described using numbers and percentages. Quantitative data were described using median (minimum and maximum) and interquartile range for non-parametric data and mean, standard deviation (SD) for parametric data after testing normality using Kolmogorov-Smirnov test or Shapiro-Wilk test. The significance of the obtained results was judged when the p-value < 0.05.

Results:

The statistical results of the socio-demographic characteristics of the studied subjects are shown in table (1). The majority of patients in the case group were males (63.33%), with no statistically significant differences among the studied groups regarding sex. There were statistically significant differences between the case and the control groups regarding age and residence ($p < 0.05$). Regarding smoking, no statistically significant differences were found between the case and control groups ($p > 0.05$).

Table (1): Statistical results of sociodemographic characteristics of the studied subjects (n=150).

	Group I (n=30)	Group II (n=60)	Group III (n=60)	Test of significance
Age (years)				
Mean ± SD Range (min-max)	46.60 ± 8.45 (33 - 68)	39.15 ± 10.55[a] (16 - 68)	39.62 ± 9.87[a] (17 - 62)	F = 6.41 p = 0.002*
Sex	**n (%)**	**n (%)**	**n (%)**	
• Males	19 (63.3)	30 (50.0)	30 (50.0)	$\chi2$ = 1.71 p = 0.425
• Females	11 (36.7)	30 (50.0)	30 (50.0)	
Residence	**n (%)**	**n (%)**	**n (%)**	
• Rural	10 (33.3)	19 (31.7)	31 (51.7)	$\chi2$ = 10.25 p = 0.006*
• Urban	20 (66.7)	41 (68.3)	29 (48.3)	
Smoking	**n (%)**	**n (%)**	**n (%)**	
• Non-smokers	16 (53.3)	34 (56.7)	36 (60.0)	$\chi2$ = 0.382 p = 0.826
• Smokers	14 (46.7)	26 (43.3)	24 (40.0)	

F: for One Way ANOVA test, SD: standard deviation, χ^2: for Chi-square test, n: number, min: minimum, max: maximum, *: Statistically significant at $p < 0.05$, similar superscripted letters denote the non-significant difference between the studied groups.

As regards the psychiatric history of the studied patients in the case and positive control groups, the majority of patients in both groups had bipolar disorder, followed by schizophrenia, with no statistically significant differences between the two studied groups regarding each of the psychiatric disorders, or the mean duration of the psychiatric illness ($p > 0.05$), (Table 2). In addition, the most frequently used antipsychotic drugs in the two groups were olanzapine, trifluoperazine, and risperidone.

Table (2): Statistical results of the psychiatric disorders distribution among group I and group II (n=90).

Psychiatric disorders	Group I (n=30) n (%)	Group II (n=60) n (%)	Test of significance
• Schizophrenia	8 (26.7)	21 (35.0)	
• Schizo-affective	5 (16.7)	9 (15.0)	MC
• Mania	10 (30.0)	1 (1.7)	p = 0.64
• Depression	5 (16.7)	2 (3.3)	
• Bipolar disorder	17 (56.7)	27 (45.0)	
Duration of psychiatric illness or antipsychotic drug therapy (years)			
Mean	4.5	5	$\chi2 = 1.16$
Range (min-max)	(2.0 - 10.0)	(1.5 - 20.0)	p = 0.244

MC: for Monte Carlo test, $\chi2$: for Chi-square test, n: number, min: minimum, max: maximum.

Serum levels of IgM and IgG anti-SNCa antibodies are shown in table (3) and figure (1). The median serum levels of both IgM and IgG anti-SNCa antibodies were significantly higher ($p < 0.05$) in the case group, compared with the positive control group, and the healthy control group.

Table (3): Statistical results of the serum anti-SNCa antibodies levels (IgM and IgG) among the studied groups (n=150).

	Group I (n=30)	Group II (n=60)	Group III (n=60)	Test of significance
	Median (min-max)	**Median (min-max)**	**Median (min-max)**	
• **IgM (ng/ml)**	38.5 (1.8 - 100)^{AB}	15.90 (0.70 - 51)^{AC}	0.2 (0.01 - 22)^{BC}	KW p < 0.001*
• **IgG (ng/ml)**	9.0 (0.7 - 75)^{AB}	4.0 (0.8 - 14)^{AC}	1.0 (0.05 - 10)^{BC}	KW p < 0.001*

KW: for Kruskal Wallis test, IgM: immunoglobulin-M, IgG: immunoglobulin-G, n: number, min: minimum, max: maximum, *: Statistically significant at $p < 0.05$, similar superscripted letters denote the non-significant difference between the studied groups with Mann Whitney U test.

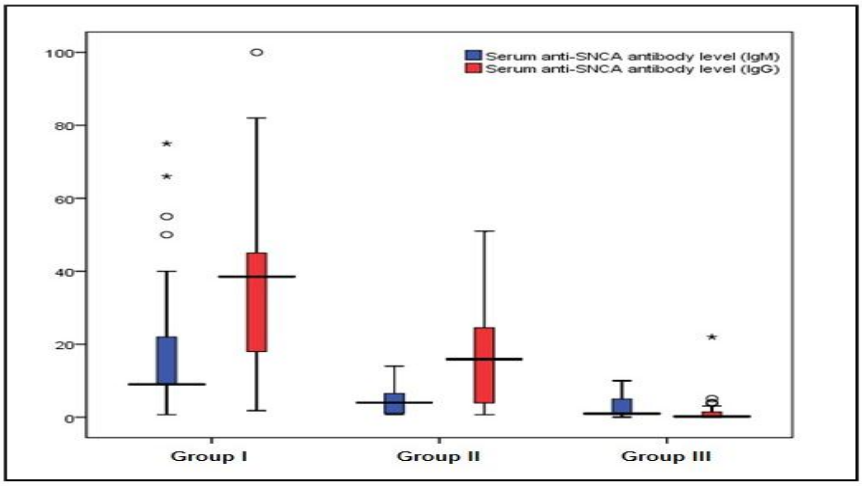

Fig. (1): Box and Whisker plot showing the median serum anti-SNCa antibodies level (IgM and IgG) (ng/ml) in the three studied groups (n = 150).

The distribution of serum levels of IgM and IgG anti-SNCa antibodies among cases with NMS according to the administered antipsychotic medications is shown in tables (4 and 5). According to these results, no statistically significant correlations were found between the median serum levels of either IgM or IgG anti-SNCa antibodies and each of the most frequently administered antipsychotic drugs, or a certain antipsychotic drug category (neither FGAs nor SGAs) among the studied cases with NMS ($p > 0.05$).

Table (4): Statistical results of the distribution of the median serum levels of IgM and IgG anti-SNCa antibodies according to the currently administered antipsychotics (by drug type) among the case group (n=30):

	IgM (ng/ml) Median (min-max)	test of significance	IgG (ng/ml) Median (min-max)	test of significance
Olanzapine				
• Not administered	9.0 (0.7 - 75)	Z = 0.155 p = 0.877	23.5 (1.8 - 56)	Z = 1.96 p = 0.05
• Administered	9.0 (0.8 - 66)		40.25 (8 - 100)	
Risperidone				
• Not administered	9.0 (0.8 - 75)	Z = 0.694 p = 0.488	29.0 (8 - 80)	Z = 0.956 p = 0.339
• Administered	9.0 (0.7 - 66)		40.0 (1.8 - 100)	
Trifluoperazine				
• Not administered	9.0 (0.7 - 66)	Z = 1.52 p = 0.129	39.5 (1.8 - 100)	Z = 0.146 p = 0.884
• Administered	9.75 (1.2 - 75)		29.0 (10.4 - 80)	

Z: for Mann Whitney U test, min: minimum, max: maximum.

Table (5): Statistical results of the distribution of the median serum levels of IgM and IgG anti-SNCa antibodies according to the currently administered antipsychotics (by drug category) among the case group (n=30):

Serum anti-SNCa antibodies	FGA only	SGAs only	Combined FGA & SGAs	test of significance
	Median (min-max)	Median (min-max)	Median (min-max)	
• **IgM (ng/ml)**	11.5 (9.0 - 25)	9.0 (0.7 - 66)	9.0 (0.8 - 75)	KW p = 0.431
• **IgG (ng/ml)**	24.4 (11.7 - 43)	38.5 (1.8 - 100)	41.0 (8.0 - 82)	KW p = 0.563

KW: for Kruskal Wallis test, χ^2: for Chi-square test, FGAs: First-generation antipsychotics. SGAs: Second-generation antipsychotics, IgM: immunoglobulin-M, IgG: immunoglobulin-G, min: minimum, max: maximum.

As illustrated in the table (6), no statistically significant correlations were found between the median serum levels of either IgM or IgG anti-SNCa antibodies and a certain psychiatric disorder among the studied cases with NMS ($p > 0.05$).

Table (6): Statistical results of the distribution of the median serum levels of IgM and IgG anti-SNCa antibodies according to the psychiatric disorders among the case group (n=30):

Psychiatric disorders	IgM (ng/ml) Median (min-max)	test of significance	IgG (ng/ml) Median (min-max)	test of significance
• Schizophrenia	4.0 (0.8 - 66)	KW p = 0.688	20.0 (0.7 - 100)	KW p = 0.967
• Schizo-affective	3.5 (0.8 - 55)		18.5 (3.5 - 51)	
• Mania	8.0 (8.0 - 8.0)		20.0 (20 - 20)	
• Depression	8.5 (7 - 10)		14.4 (11 - 17.8)	
• Bipolar disorder	5.5 (0.7 - 75)		22.0 (1.1 - 82)	

KW: for Kruskal Wallis test, min: minimum, max: maximum.

The present work demonstrated that the median serum levels of both IgM and IgG anti-SNCa antibodies were found to be significantly higher among male patients with NMS, compared with females ($p < 0.001$), as illustrated in the table (7).

Table (7): Statistical results of the distribution of the median serum levels of IgM and IgG anti-SNCa antibodies among male and female psychiatric patients in the case group (n=30):

Patients' Sex	IgM (ng/ml) Median (min-max)	test of significance	IgG (ng/ml) Median (min-max)	test of significance
• Males	5.0000 (0.70 - 40.00)	Z = 2.40 p = 0.0168*	11.7000 (0.01 - 80.00)	Z = 2.51 p = 0.012*
• Females	2.0000 (0.05 - 75.00)		2.8000 (0.01 - 100.00)	

Z: for Mann Whitney U test, *: Statistically significant at $p < 0.05$, min: minimum, max: maximum.

Regarding the diagnostic value of serum levels of anti-SNCa antibodies (IgM and IgG) in the prediction of NMS among the studied groups, table (8) and figure (2) illustrates that when comparing group I with group II, the median serum IgM level demonstrated 80.0% sensitivity and 83.3% specificity at a cut-off point 8.5 (AUC=0.780), while the median serum IgG level demonstrated 70.0% sensitivity and 70.0% specificity at a cut-off point 22.5 (AUC=0.762). There were statistically highly significant differences between the two studied groups as regards both serum IgM and IgG antibodies levels ($p < 0.001$).

When comparing group I with group III, as shown in table (8) and figure (3), the median serum IgM level demonstrated 83.3% sensitivity and 83.3% specificity at a cut-off point 7.0 (AUC=0.804), while the median serum IgG level demonstrated 96.7% sensitivity and 98.3% specificity at a cut-off point 6.55 (AUC=0.990). There were statistically highly significant differences between the two studied groups as regards both serum IgM and IgG antibodies levels ($p < 0.001$).

On the other hand, as revealed in table (8) and figure (4), when comparing group II with group III, the median serum IgM level demonstrated 71.7% sensitivity and 55.0% specificity at a cut-off point of 1.25 (AUC=0.640), while the median serum IgG level demonstrated 96.7% sensitivity and 83.3% specificity at a cut-off point 6.55 (AUC=0.956). There were statistically significant differences between the two studied groups as regards both serum IgM and IgG antibodies levels ($p < 0.001$).

Table (8): The validity of serum levels of IgM and IgG anti-SNCa antibodies levels in the prediction of the neuroleptic malignant syndrome among the studied groups:

	AUC (95% CI)	p-value	Cut-off point	Sensitivity (%)	Specificity (%)
Group I compared with Group II					
• **IgM**	0.780 (0.661 - 0.899)	< 0.001*	8.5	80.0	83.3
• **IgG**	0.762 (0.653 - 0.871)	< 0.001*	22.5	70.0	70.0
Group I compared with Group III					
• **IgM**	0.804 (0.699 - 0.912)	< 0.001*	7.0	83.3	83.3
• **IgG**	0.990 (0.975 - 1.0)	< 0.001*	6.55	96.7	98.3
Group II compared with Group III					
• **IgM**	0.640 (0.540 - 0.740)	0.008*	1.25	71.7	55.0
• **IgG**	0.956 (0.922 - 0.990)	< 0.001*	1.65	96.7	83.3

AUC: Area under the curve, CI: Confidence interval, IgM: immunoglobulin-M, IgG: immunoglobulin-G, *: Statistically significant at $p < 0.05$, serum IgG & IgM levels are described as median (minimum-maximum).

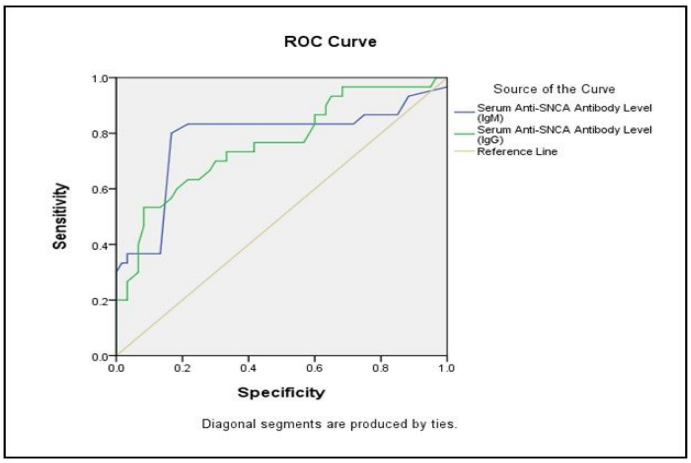

Fig. (2): A receiver operating characteristics curve to detect the diagnostic value of serum IgM and IgG anti-SNCa antibodies levels in the prediction of the neuroleptic malignant syndrome, when comparing between group I and group II.

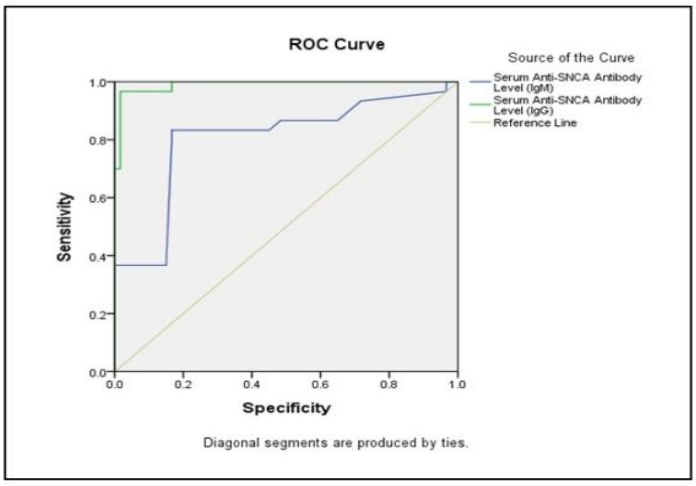

Fig. (3): A receiver operating characteristics curve to detect the diagnostic value of serum IgM and IgG anti-SNCa antibodies levels in the prediction of the neuroleptic malignant syndrome, when comparing between group I and group III.

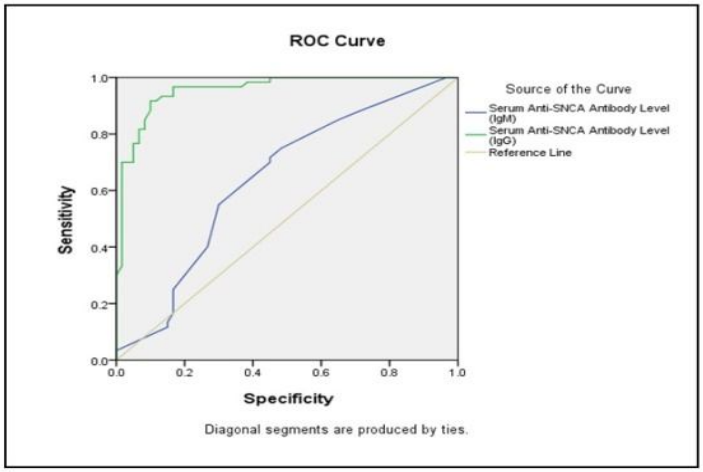

Fig. (4): A receiver operating characteristics curve to detect the diagnostic value of serum IgM and IgG anti-SNCa antibodies levels in the prediction of the neuroleptic malignant syndrome, when comparing between group II and group III.

Discussion:

Since its discovery, α-syn protein has become one of the most important neuronal cytoskeletal proteins, particularly with its close association with chronic neuro-degenerative brain disorders (Bengoa-Vergniory et al., 2017).

Up till now, most human and animal studies regarding α-syn protein have focused on the biological functions of this protein and its role in dopamine biosynthesis regulation or its interaction with dopamine receptors. In addition, several studies have investigated the relationship between anti-SNCa auto-antibodies and the development of chronic neurodegenerative brain disorders, such as AD, PD, and LBD. To our knowledge, no previous studies have been conducted to investigate the direct relationship between anti-SNCa antibodies and the development of acute emergencies, such as NMS. Hence, the strength of this study is that it is the first study focusing on this point of interest.

The current study found that the risk for occurrence of NMS was higher among young male patients, with statistically significant differences between the case and the control groups, regarding age.

The present results are consistent with a previous meta-analysis conducted by Gurrera

(2017). They showed a predominance of males in most (75%) estimates with an overall median sex ratio of 1.47 (95% CI, range: 1.20-1.80). In addition, the study found that NMS incidence peaked at age 20-25 years and declined steadily thereafter.

The relatively high incidence of NMS among men was explained by different suggestions. One explanation was that men aged 25-91 years have 48% greater skeletal muscle mass than comparably aged women. Greater muscle mass in men might produce more noticeable rigidity or higher metabolism leading to more extreme body temperature (Strugnell et al., 2014).

Moreover, antipsychotic medication exposure may differ among men and women. Several studies have found that psychotic disorders, and specifically schizophrenia, are more prevalent in men (Bergen et al., 2014). Furthermore, several studies have shown that men usually require higher doses of antipsychotic medications to achieve comparable clinical effects (Velamoor, 2017).

The current results revealed that the majority of patients in the case group and positive control group had bipolar disorder, followed by schizophrenia, with no statistically significant differences between the two studied groups regarding each of the complained psychiatric disorders. In addition, the mean duration of the psychiatric illness, and in turn that of the antipsychotic therapy was 4.5 years in the case group, compared with 5 years in the positive control group. The most frequently administered antipsychotic drugs in both the case and positive control groups were olanzapine, trifluoperazine, and risperidone. In particular, the majority of patients in the two groups were maintained on SGAs (atypical neuroleptics), either alone or combined with FGAs (typical neuroleptics). No statistically significant differences were found between the two groups regarding each of the psychiatric disorders, the mean duration of the psychiatric illness, or the mean duration of the antipsychotic drug therapy.

The relationship between antipsychotic drug exposure and neuronal cytotoxicity, including oxidative stress, apoptosis, and neurodegeneration has become a point of concern in several experimental studies. For instance, Singh et al. (2016) conducted a study to assess the effects of prenatal exposure to risperidone on neurotoxicity in rat offspring. They found significant stunting of fetal brain weight, a substantial reduction in the thickness of neocortical layers, and apoptotic neurodegeneration in fetal brains, as well as the long-lasting impact on anxiety, like impaired behavioral responses on explorative mazes.

According to previous experimental studies, the present study hypothesizes that chronic exposure to antipsychotics may result in neurodegenerative changes in the brain parenchyma, leading to accumulation of misfolded proteins, including α-syn protein (Singh et al., 2016). These proteins leak into the CSF and reach the circulation through the damaged blood-brain barrier. These leaked proteins act as auto-antigens that stimulate the immune system to produce autoantibodies against them (Kobeissy and Moshourab, 2015).

The most important auto-antibodies are the memory antibodies IgG (half-life, 23 days) accounting for approximately 70% of the total immunoglobulins. Since IgG autoantibodies against the released proteins will last a much longer period than the proteins themselves, serum autoantibodies had been used as biomarkers for brain injury in the blood instead of the native proteins, either in the CSF or in peripheral blood (Abou-Donia et al., 2014).

In the current study, although IgM was found to be significantly higher than IgG in

the case group, both IgM and IgG were significantly higher in the case group, compared with the control groups.

The current findings can be explained by the physiological fact that IgM antibodies are produced from plasma cells in small amounts during the primary immune response; as a result of the first exposure to a certain antigen, and then with recurrent exposure to the same antigen, the secondary immune response leads to release of large amounts of IgG antibodies from plasma cells. This fact means that the presence of IgM antibodies indicates recent (acute) exposure to the antigen, while IgG antibodies indicate old (chronic) antigenic exposure (El-Fawal, 2014). This is why the serum levels of IgM anti-SNCa antibodies are significantly higher in the cases presenting with NMS, which is an acute emergency condition, compared with the other control groups.

In other words, the relatively higher serum levels of IgM antibodies in the case group, compared with serum levels of IgG antibodies may be an indicator of the occurrence of a recent acute significant brain damage that could precipitate NMS. On the other hand, the presence of relatively lower serum levels of IgG antibodies in the case group and the positive control group can indicate old recurrent minute unnoticed degenerative changes over time of exposure to antipsychotics that were not significant enough to induce NMS in such patients.

This finding confirms several other studies that have focused on the chronic neurodegenerative brain disorders that may precipitate NMS, such as AD, PD, and LBD (Shalash et al., 2017). They found that serum levels of IgG anti-SNCa antibodies were significantly higher in the affected patients, compared with the normal healthy controls.

According to the results of the present work, statistically high significant correlations were found between the median serum levels of both IgM and IgG anti-SNCa antibodies and the patients' sex among the studied cases with NMS, being significantly higher among males patients.

This finding can explain the predominance of NMS among male patients, either in the current study or in previous studies. In simple words, this finding means that the incidence of the proposed antipsychotics-induced brain damage and neuronal cytotoxicity was much higher among psychiatric male patients, causing higher serum levels of anti-SNCa antibodies, as well as a higher incidence of NMS among those patients, confirming the hypothesis of the current study.

On the other hand, the present results revealed that the increased IgM and IgG antibodies, as biomarkers for brain damage, in patients with NMS cannot be attributed to a certain antipsychotic drug or a specific neuroleptic category, either typical or atypical. Also, no statistically significant correlations were found between the median serum levels of either IgM or IgG anti-SNCa antibodies and a certain psychiatric illness among psychiatric patients either in the case group or in the positive control group.

From the findings of this work, it can be concluded that significant associations were identified between increasing serum levels of IgM and IgG anti-SNCa antibodies, chronic antipsychotic drug intake, and development of NMS among psychiatric patients and that these antibodies can be used as predictor markers for brain damage, with high sensitivity and specificity, in patients presenting with NMS.

Recommendations:

According to the findings of the present study, certain precautions and

recommendations, directed to both healthcare providers and researchers, should be considered to lower the risk of development of NMS:

(1) More research is recommended to elucidate the mechanism of this antipsychotic-induced brain damage.

(2) It is recommended to search for more biomarkers for antipsychotic-induced brain damage.

(3) It is recommended to search for mechanisms behind the increased incidence of NMS in males.

(4) Increase awareness of physicians about risks of NMS in patients on antipsychotics to lower its incidence.

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Conflict of interest:

All authors confirm that there are no declarations of interest. **Amal A. El-Bakary** is one of the coauthors and the managing editor of the Mansoura Journal of Forensic Medicine & Clinical Toxicology journal. She declares that she did not review the paper nor was included in the team handling the paper till acceptance by independent reviewers who were blind about the authors of the paper.

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العقاقير المضادة للذهان وخطر الإصابة بمتلازمة الذهان الخبيثة بين عينة من المرضى النفسيين المصريين: دور الألفا- ساينوكلين كمؤشر حيوي لتلف الدماغ

د. محمد العدل موسى ، أ.د. عبد العزيز غانم ، أ.م.د. أسامة شبكة ، أ.م.د. شيماء محمود مطاوع ، أ.د. أمال عبد السلام البقري

قسم الطب الشرعي والسموم الإكلينيكية - كلية الطب - جامعة المنصورة

تعد متلازمة الذهان الخبيثة إحدى حالات الطوارىء العصبية المميتة، والتي غالباً ما تحدث كرد فعل غير طبيعي ومفاجيء من الجهاز العصبي تجاه العقاقير المضادة للذهان. على الجانب الآخر، يعتبر بروتين ألفا-ساينوكلين البشري أحد البروتينات الهامة والمرتبطة بالهيكل الخلوي العصبي، والذي ارتبط مؤخراً بحدوث العديد من الاضطرابات العصبية التنكسية المزمنة، مثل مرض الشلل الرعاش. أجريت الدراسة الحالية لتقييم العلاقة بين مستويات الأجسام المضادة لبروتين ألفا-ساينوكلين (IgM & IgG) بمصل الدم (السيرم) وخطر حدوث متلازمة الذهان الخبيثة لدى المرضى النفسيين الذين يتناولون العقاقير المضادة للذهان، وكذا للتحقق من القيمة التشخيصية لتلك الأجسام المضادة كمؤشرات حيوية محتملة لتشخيص تلف الدماغ الناجم عن تناول العقاقير المضادة للذهان لدى المرضى النفسيين الذين يعانون من متلازمة الذهان الخبيثة. أجريت هذه الدراسة على ١٥٠ شخصاً تم تقسيمهم إلى ثلاث مجموعات. تضمنت المجموعة الأولى (مجموعة الحالات) ٣٠ مريضاً نفسياً ممن يتلقون العقاقير المضادة للذهان، والذين يعانون من متلازمة الذهان الخبيثة، بينما اشتملت المجموعة الثانية (مجموعة ضابطة إيجابية) على ٦٠ مريضاً نفسياً من المتلقين للعقاقير المضادة للذهان، والذين لم يعانون مسبقاً من متلازمة الذهان الخبيثة خلال تاريخهم المرضي. أما المجموعة الثالثة (مجموعة ضابطة سلبية) فقد تضمنت ٦٠ شخصاً من المتطوعين الأصحاء. تم قياس مستويات الأجسام المضادة (IgM & IgG) في مصل الدم باستخدام تقنية الفحص المناعي الإنزيمي (ELIZA). وكشفت الدراسة أن متوسط مستويات الأجسام المضادة لبروتين ألفا-ساينوكلين (IgM & IgG) بمصل الدم كان أعلى بشكل ملحوظ لدى مرضى مجموعة الحالات، مقارنة بكل من المجموعتين الضابطتين، بالإضافة إلى وجود فروق ذات دلالة إحصائية عالية بين المجموعات الثلاث محل الدراسة فيما يتعلق بمتوسط مستويات تلك الأجسام المضادة بمصل الدم ($p < 0.001$). من تلك النتائج نستخلص وجود علاقة ذات دلالة إحصائية بين زيادة مستويات الأجسام المضادة لبروتين ألفا-ساينوكلين (سواء IgM أو IgG) بمصل الدم من ناحية، وكل من التناول المزمن للعقاقير المضادة للذهان، وإمكانية حدوث متلازمة الذهان الخبيثة لدى المرضى النفسيين المتلقين لتلك العقاقير من ناحية أخرى، بالإضافة إلى إمكانية استخدام تلك الأجسام المضادة كمؤشرات تنبؤية لتلف الدماغ الناجم عن تناول العقاقير المضادة للذهان لدى المرضى النفسيين الذين يعانون من متلازمة الذهان الخبيثة.