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Lowered serum cesium levels in schizophrenia: association with immune-inflammatory biomarkers and cognitive impairments.

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Abstract

OBJECTIVE: A previous study showed that schizophrenia is accompanied by lowered levels of trace/metal elements including cesium. There are no data whether changes in cesium, rubidium and rhenium are associated with activated immune-inflammatory pathways, cognitive impairments, and the symptomatology of schizophrenia.

METHODS: This study measured cesium, rubidium, and rhenium, cognitive impairments (using the Brief Assessment of Cognition in Schizophrenia) and the cytokines/chemokines interleukin (IL)-1β, tumor necrosis factor (TNF)-α, and CCL11 (eotaxin) in 120 schizophrenia patients and 54 healthy controls. Severity of illness was assessed using the Brief Psychiatric Rating Scale (BPRS), the Scale for the Assessment of Negative Symptoms (SANS), the Fibromyalgia and Chronic Fatigue Syndrome Rating (FF) Scale and the Hamilton Depression Rating Scale (HAM-D).

R**ESULTS:** Serum cesium was significantly lower in schizophrenia patients as compared with controls. Serum cesium was significantly and inversely associated with CCL11 and TNF-α, but not IL-1β. Moreover, there were significant inverse associations between serum cesium levels and the BPRS, FF, HAM-D and SANS scores and positive correlations between cesium and neurocognitive probe results including the Tower of London, Symbol Coding, Controlled Word Association, Category Instances, Digit Sequencing Task, and List Learning tests.

CONCLUSION: The results suggest that lowered serum cesium levels may play a role in the pathophysiology of SCZ, specific symptom domains including negative, depressive and fatigue symptoms, neurocognitive impairments (spatial working, episodic and semantic memory and executive functions) and neuro-immune pathways as well.

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Introduction

Schizophrenia (SCZ) is a severe and debilitating mental illness which is characterized by negative and positive symptoms and neurocognitive impairments affecting about 1% of the world population[1]. A biological predisposition with multi-genetic risk factors, changes in neurotransmitter systems, neuroimmune factors and psychosocial stress are associated with an increased risk for schizophrenia[2]. The first comprehensive neuro-immune theory of SCZ was introduced in 1995 by Smith and Maes as the "macrophage-lymphocyte theory" considering that T lymphocytes and activated macrophages are key phenomena in the pathophysiology of SCZ[3]. Since them many publications confirmed that schizophrenia is accompanied by activation of the immune-inflammatory response system (IRS) and compensatory immune-regulatory system (CIRS)[4-6]. Furthermore, recent studies showed attenuated levels of antioxidants[7] including enzymatic antioxidant activities and some trace elements[8-10].

Recently, some research papers reported that SCZ is accompanied by changes in trace/metal elements although the results were contradictory depending on the type of metals, type of SCZ, and methods[11-15]. Importantly, Cai et al. found a significant reduction in serum levels of the alkali metal cesium in SCZ patients in comparison with healthy controls [15]. This may be important because cesium shares some similarities with potassium and, therefore, may interfere with potassium metabolism [16] while there is some evidence that the KCNH2 SNP, which encodes the pore-forming subunit of potassium channels, is associated with schizophrenia and with cognitive impairments [17]. Moreover, cesium, rhenium, and rubidium were previously assayed in sera of patients with another immune-inflammatory illness, namely rheumatoid arthritis, and of those three metals cesium was found to be decreased in patients as compared with healthy controls [18]. Cesium is a non-essential element in the body and 1.6 mg of Cs is distributed in muscle, bone

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and blood [19]. In mice, a central nervous system (CNS)-active carborane containing cesium has antidepressant effect by inhibiting pore formation by the cation-selective purinergic receptor ion channel [20]. Like potassium, high levels of rubidium are found in red blood cells, viscera and muscle tissues [21] while rubidium also shares some chemical properties with potassium and may replace potassium in the Na^+-K^+-ATPase system while K^+-dependent ATPase is activated by low rubidium concentrations [22]. Like potassium, rubidium may stimulate human metabolism due to its chemical similarities to K^+ [21]. Rhenium has no known biological functions although rhenium containing compounds are highly toxic [23]. Only few studies focused on the above-mentioned elements in SCZ although two of these metals, namely cesium and rubidium, play a role in biological systems and one of these, namely cesium, is associated with immune-inflammatory conditions.

Thus, the present study measured cesium, rhenium and rubidium in SCZ patients in order the estimate the associations between these metals and immune biomarkers (IL-1β, TNF-α, and CCL11), the symptom subdomains of SCZ (including depression), and neurocognitive impairments.

Materials and Methods

Participants

This study included 120 patients with SCZ and 54 healthy controls recruited at the Ibn-Rushd Training Hospital for Psychiatric Medicine, Baghdad, Iraq (December 2018 until February 2019). The Fifty-four apparently healthy controls were staff members or their family members and friends of SCZ patients. SCZ patients were in a stabilized phase of illness and did not show acute psychotic episodes for at least one year prior to the study. DSM-IV-TR criteria were used to make the diagnosis of SCZ[24]. Healthy controls were excluded when they presented with a lifetime or

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current DSM-IV-TR axis I diagnosis or when they showed a positive family history of psychosis. SCZ patients were excluded when they suffered from acute psychotic episodes the year prior to the study or axis-1 DSM-IV-TR disorders other than SCZ, including bipolar disorder, major depression, schizoaffective disorder, OCD, psycho-organic disorders, and substance use disorders. All subjects had C-reactive protein (CRP) values <6 mg/L indicating that no overt inflammation was present. Exclusion criteria for SCZ patients and healthy controls were: a) use of supplements with antioxidants or ω3-polyunsaturated fatty acids the month prior to the study; b) lifetime use of immunosuppressive drugs including glucocorticoids; c) neurodegenerative and neuro-inflammatory disorders including stroke, Parkinson's disease, multiple sclerosis and Alzheimer's disease; and d) (auto)immune illnesses including psoriasis, rheumatoid arthritis, COPD, inflammatory bowel disease, and diabetes mellitus.

The study was conducted according to Iraq and International ethics and privacy laws. Written informed consent was obtained from all participants as well as the first-degree relatives of SCZ participants (the legally authorized representatives are father, mother, spouse, son or brother) prior to participation in this study. Approval for the study was obtained from the ethics committee (IRB) of the College of Science, University of Kufa, Iraq (347/2019), which is in compliance with the International Guideline for Human Research protection as required by the Declaration of Helsinki.

Measurements

Clinical assessments

A senior psychiatrist specialized in SCZ used a semi-structured interview to assess socio-demographic and clinical data in patients and healthy controls. The psychiatrist made the diagnosis

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of SCZ employing the DSM-IV-TR diagnostic criteria using the Mini-International Neuropsychiatric Interview (M.I.N.I.) in a validated Arabic translation (Iraqi dialect). The same psychiatrist also assessed the schedule for the deficits syndrome (SDS) [24], the Scale for the Assessments of Negative Symptoms (SANS) [25], the Brief Psychiatric Rating Scale (BPRS) [26], the Hamilton Depression Rating Scale (HAMD) [27] and the Rating Scale for Fibromyalgia and Chronic Fatigue Syndrome (the Fibro-Fatigue or FF scale [28]. On the same day, a research psychologist, blinded to the clinical diagnosis, assessed neuropsychological probes using the Brief Assessment of Cognition in Schizophrenia [29]. The latter battery includes the List Learning test (to assess verbal episodic memory), Digit Sequencing Task (to assess working memory), Category Instances (to assess semantic fluency) and Controlled Word Association (to assess letter fluency), Symbol Coding (to assess attention) and Tower of London (to assess executive functions). We also assessed the drug state of the patients because 68 patients were treated with fluphenazine, 108 with risperidal and 11 with olanzapine. The diagnosis of tobacco use disorder (TUD) was made using the DSM-IV-TR criteria. Body mass index (BMI) was assessed the same day as the clinical interview and was scored as body weight (kg) / length (m^2).

Assays

Fasting (> 8 hours) venous blood (5 ml) was aspirated between 8:00 and 10:00 a.m. from patients and controls utilizing disposable needles and plastic syringes and samples were transferred into a clean plain tube. Blood was left at room temperature for 15 min for clotting and centrifuged 3000 rpm for 10 min, and then serum was separated and transported into two Eppendorf tubes to be stored at − 80 °C until analyzed. Commercial ELISA sandwich kits were used to measure serum CCL11, IL-1β, and TNF-α (Elabscience®, Inc. CA, USA). All measured concentrations of CCL11

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(sensitivity=9.38 pg/mL), IL-1β (sensitivity=4.69pg/mL), and TNF-α (sensitivity=4.69 pg/mL) were greater than the sensitivity of the assays. We did not apply left-censoring and used the measured concentration in the statistical analyses. The procedures were followed exactly without modifications according to the manufacturer's instructions. The intra-assay coefficient of variation (CV) (precision within an assay) were < 6.22%. Serum CRP was measured using a kit supplied by Spinreact®, Spain. The test is based on the principle of latex agglutination.

Estimation of Serum Metals

The concentrations of cesium, rubidium, and rhenium in the serum samples of SCZ patients and controls were measured by using graphite furnace atomic absorption spectrophotometer (Shimadzu model GFA-6200) at the labs of the Ministry of Science and Technology/Department of Research of Biochemical Science, Baghdad, Iraq. The measurements occurred at the specific wavelengths of each ultra-trace element. Standard solutions of the three metals were obtained from Sigma-Aldrich in a concentration of 1000 μg/l each, and subsequent dilutions were carried out to obtain a calibration curve. All other reagents used were of AAS grade, and deionized water was used to ensure no leaching of any TEs to the measured standard and samples. Small screw-capped polyethylene containers were used for the preparation of the samples and all analyses were carried out as mentioned previously [30] with some modifications [18]. Briefly, the deep-frozen serum samples were reconstituted at room temperature and then centrifuged at 2000 g for 15 min. Two hundred fifty microliters of serum were diluted into 1:8 (v/v) up to 2 ml with 0.5% (v/v) HNO_3 for AAS measurements supplied by CPAchem Ltd., (Stara Zagora, Bulgaria) and internal standard solutions. The three metal element standards were mixed in the calibration solutions and diluted with the same nitric acid solution and internal standard solutions and then prepared in

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concentrations corresponding with the concentrations of the trace elements in human serum. The certified reference materials used for internal quality control number 92091 that contains 33 elements at concentrations of 10 mg/l of 10% HNO_3 (TraceCERT®, Sigma-Aldrich) were diluted according to the instructions of products, further prepared with 0.5% HNO_3 (v/v). The percentage recovery of the measured metal concentrations was within the range of 90–98% of the certified values of the elements.

Statistical Analysis

The differences in the scale variables, namely immune biomarkers and metal elements, were assessed using analysis of variance or the Mann-Whitney U test (in case of heterogeneity of variance) while associations among two sets of categorical variables were assessed using analysis of contingency tables (χ^2 tests). Correlations between scale variables were checked using Pearson's product moment correlations or partial correlations. We used univariate and multivariate GLM analysis to examine the associations between explanatory variables and the three trace elements, while adjusting for age, sex, BMI and drug state. Tests for between-subject effects were used to examine the associations between the significant explanatory variables and the elements. Multiple tests were p-corrected using the false discovery rate (FDR) method. All tests were two-tailed and a p-value of 0.05 was used for statistical significance. IBM SPSS25 for windows was used to analyze the data.

Results.

Socio-demographic data

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Table 1 shows the socio-demographic data of the SCZ patients in comparison with healthy controls. There were no statistically significant differences in sex, TUD, marital status, residency, and BMI between SCZ patients and normal controls. Significantly more patients were unemployed as compared with controls while years of education were slightly lower in SCZ patients. SCZ patients were somewhat older than controls and showed a lower level of education. The BPRS, SANS, FF and HAM-D scores were significantly higher in patients than in controls. CCL11, IL-1β, and TNF-α were significantly higher in SCZ patients as compared with healthy controls. All cognitive test scores were significantly lower in patients than controls.

Intercorrelations

In the whole study group, there were significant correlations between cesium and the total BPRS score ($r=-0.269$, $p<0.001$), SANS ($r=-0.247$, $p<0.001$), FF scale ($r=-0.234$, $p=0.002$) and the HAM-D ($r=-0.262$, $p<0.001$, all $n=174$). Serum cesium levels were also correlated with the results of cognitive probes namely Tower of London ($r=0.221$, $p=0.003$), Symbol Coding ($r=0.276$, $p<0.001$), COWA ($r=0.266$, $p<0.001$), Category Instances ($r=0.19$, $p=0.012$), Digit Sequencing Task ($r=0.225$, $p=0.003$), and List learning ($r=0.195$, $p=0.010$). Cesium was significantly correlated with CCL11 ($r=-0.210$, $p=0.006$), and TNF-α ($r=-0.198$, $p=0.01$), but not with IL-1β ($r=-0.09$, $p=0.237$). All the above-mentioned significant associations remained significant after p-correction for FDR and controlling for age, sex and BMI in partial correlation analyses. **Figure 1** shows the association (partial regression) between cesium levels and CCL11. There were no significant associations between the other trace elements and the biomarkers or clinical data.

Differences in biomarkers between the study groups

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Table 2 displays the outcome of a multivariate GLM analysis comparing the three trace elements between the study groups while adjusting for age, BMI, and sex. There were significant differences in those elements between the study groups with an effect size of 0.074, while the covariates had no significant effects. Tests for between-subject effects and **Table 1**, which shows the estimated marginal mean (SE) values, indicates that cesium was significantly lower in SCZ patients as compared with controls and that the two other trace elements did not differ between the groups. The differences in cesium remained significant after p-correction (p=0.009).

Effects of background variables.

As shown above, age, sex, and BMI had no significant effects on serum biomarker levels. TUD also had no significant effect on the measured biomarker levels (F=0.66, df=3/166, p=0.576, partial η^2 =0.012). We also examined the possible effects of antipsychotic drug administration and using multivariate GLM analysis and tests for between-subjects, we found no significant effects of use of risperidone (F=0.731, df=3/166, p=0.535, partial η^2=0.013), olanzapine (F=0.538, df=3/166, p=0.657, partial η^2 =0.010) and fluphenazine (F=0.403, df=3/166, p=0.732, partial η^2 =0.008) on the three metals even without p correction for FDR.

Discussion

The first major finding of this study is that serum cesium is significantly lowered in SCZ while no significant changes in serum rhenium and rubidium were observed. These results extend those of Cai et al. who found a significant reduction in serum cesium in SCZ [15]. As described in the Introduction, there is evidence that cesium shares similarities with potassium and competes with potassium for both active and passive membrane transport[31], although, after intake, cesium is

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distributed somewhat differently and exhibits a substantially longer whole-body retention time than potassium [31]. Moreover, changes in the permeability of the brain-CSF barrier may occur in response to trace elements including cesium as observed in Alzheimer's disease [32]. In this respect, Leggett et al. found that the plasma cesium/brain cesium ratio is 0.424 [33], indicating that cesium accumulates in the brain.

The second major finding of this study is the significant correlation among cesium levels and different symptom subdomains and cognitive impairments including semantic memory, excutive functions, spatial memory, episodic memory and attention. These results further suggest that lowered cesium may contribute to the phenome of SCZ [34]. Interestingly, in patients with Alzheimer's disease, cesium (and rubidium) concentrations were significantly lowered as compared with controls whilst plasma and cerebrospinal fluid cesium levels were strongly correlated [32]. In CA1 hippocampal glial cells, cesium prevents maintenance of long-term depression thereby affecting synaptic plasticity through blockade of potassium uptake [35]. Moreover, cesium may also have some neuroprotective properties by inhibiting GSK3β, preventing caspase-3 activation and neuronal apoptosis, and attenuating peroxide-induced cell death [36]. These authors, therefore, conclude that given its good blood-brain-barrier penetration [33], cesium may have some use in the treatment of neurodegenerative disorders.

The third major finding of our study is that the levels of cesium are significantly and inversely associated with immune biomarkers namely CCL11 and TNF-α, but not IL-1β although all three cytokines/chemokines are increased in SCZ. Interestingly, Cai et al. [17] reported that the lowered cesium levels in SCZ are associated with lowered zinc and selenium concentrations. This is an important finding because lowered zinc is an established immune-inflammatory biomarker associated with psychiatric diseases including depression [37] and SCZ [38] and because selenium has

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antioxidant and anti-inflammatory properties [39]. Moreover, a previous study in rheumatoid arthritis reported a decrease in cesium, but not rubidium or rhenium[18], suggesting that this metal profile is a response to activated immune-inflammatory pathways. Future research should examine whether lowered cesium could be the consequence of immune activation in SCZ or may play a role in the neuro-immune pathophysiology of that disorder.

Conclusions

Serum cesium is decreased in SCZ while no significant changes of rhenium and rubidium could be found. The lowered levels of cesium are associated with cognitive impairments, severity of schizophrenia symptoms domains and inflammatory biomarkers (CCL11 and TNF-α). These findings suggest that cesium may play a role in the pathophysiology of schizophrenia for example by inference with potassium channels, immune-inflammatory pathways, lowered neuroprotection or synaptic plasticity.

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Conflict of interest

The authors declare that there is no conflict of interest.

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Author's contributions

All the contributing authors have participated in preparation of the manuscript.

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Figure 1. Partial regression plot of cesium (Cs) on CCL11 (eotaxin) levels showing a significant inverse association between both variables (t=-2.21, p=0.028).

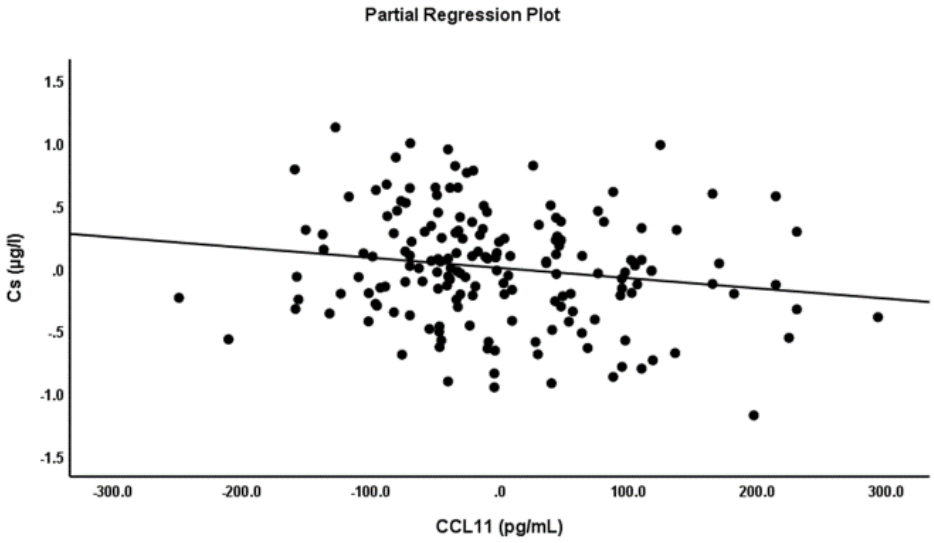

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Table 1: Demographic, clinical and biomarker data in healthy controls (HC) and schizophrenia (SCZ) patients.

Variables	Control N=54	SCZ N=120	F/χ^2	df	p
Sex (F/M)	18/36	48/72	0.703	1	0.402
TUD (Y/N)	17/37	42/78	0.206	1	0.650
Marital status (M/S)	23/31	53/65	0.081	1	0.776
Residency Urban/Rural	52/2	104/16	3.723	1	0.054
Employment (Y/N)	50/4	22/98	84.663	1	<0.001
Age (years)	37.6±10.50	41.0±9.7	4.422	1/172	0.037
BMI (kg/m^2)	26.9±3.83	26.7±4.8	0.066	1/172	0.798
Education (years)	14.3 (4.9)	12.3 (4.2)	7.599	1/172	0.007
BPRS	18.0±0	63.7±14.0	MWU	-	<0.001
SANS	1.04±0.6	91.1±16.6	MWU	-	<0.001
HAM-D	0.0	29.1 (8.1)	MWU	-	<0.001
FibroFatigue scale	0.0	23.9 (4.3)	MWU	-	<0.001
IL-1β (pg/mL)	0.75±0.30	1.92±0.94	MWU	-	<0.001
TNF-α (pg/mL)	38.77±22.83	60.44±14.12	MWU	-	<0.001
CCL11 (pg/mL)	138.88±57.25	281.59±81.64	MWU	-	<0.001
List learning	59.37±7.47	25.65±9.94	MWU	-	<0.001
Digit Sequencing Task	17.00±4.18	4.32±2.95	MWU	-	<0.001
Category Instances	70.28±6.25	32.58±17.70	MWU	-	<0.001
COWA	33.26±3.33	6.17±4.05	MWU	-	<0.001
Symbol Coding	79.39±7.84	18.21±14.80	MWU	-	<0.001
Tower of London	19.61±1.83	6.32±4.54	MWU	-	<0.001
Rb (µg/l) *	0.54±0.35	0.65±0.38	3.307	1/169	0.071
Cs (µg/l) *	1.14±0.46	0.93±0.43	8.819	1/169	0.003
Re (µg/l) *	0.04±0.02	0.04±0.03	0.511	1/169	0.475

All data are shown as mean ±SD; except *: model-generated estimated matginal means (SE) obtained by the univariate GLM analyses shown in Table 2.

TUD: Tobacco use disorder

BPRS: The Brief Psychiatric Rating Scale

SANS: Scale for the Assessment of Negative Symptoms

HAM-D: The Hamilton Depression Rating Scale

IL: Interleukin

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TNF: Tumor necrosis factor

CCL11: eatoxin

Rb: Rubidium

Cs: Cesium

Re: Rhenium

BMI: Body mass index.

COWA: Controlled Oral *Word* Association Test

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Table 2: Results of multivariate GLM analysis showing the associations between biomarkers and diagnosis while adjusting for background variables

Type	Dependent variable	Explanatory variable	F	df	p	Partial η^2
Multivariate	Cs, Rb, Re	Diagnosis	4.466[b]	3/167	0.005	0.074
		Sex	0.876[b]	3/167	0.455	0.015
		Age	0.321[b]	3/167	0.810	0.006
		BMI	0.245	3/167	0.865	0.004
Tests of Between-Subjects Effects	Cs	Diagnosis	8.809	1	0.003	0.050
	Rb	Diagnosis	3.307	1	0.071	0.019
	Re	Diagnosis	0.511	1	0.475	0.003

Diagnosis: schizophrenia patients versus healthy controls

Rb: Rubidium

Cs: Cesium

Re: Rhenium

BMI: Body mass index.