Psychiatry Research 238 (2016) 333–337

Contents lists available at ScienceDirect

Psychiatry Research

journal homepage: www.elsevier.com/locate/psychres

The association between serum creatine kinase, mood and psychosis in inpatients with schizophrenia, bipolar and schizoaffective disorders

Sarah Hollander [a,*], Eldar Hochman [a,b], Gal Shoval [a,b], Michal Taler [a,c], Sharon Trommer [a], Haggai Hermesh [a,b], Abraham Weizman [a,b,c], Amir Krivoy [a,b,c]

[a] Sackler Faculty of Medicine, Tel-Aviv University, Israel
[b] Geha Mental Health Center, Israel
[c] Laboratory of Biological Psychiatry, Felsenstein Medical Research Center, Israel

ARTICLE INFO

Article history:
Received 11 May 2015
Received in revised form
19 November 2015
Accepted 26 January 2016
Available online 3 February 2016

Keywords:
Creatine kinase
Affect
Mood disorders
Psychotic disorders
Bipolar disorder
Depression
Psychopathology

ABSTRACT

Previous studies demonstrated levels of serum CK (sCK) in the majority of patients undergoing acute psychosis. Records of 1054 patients hospitalized in Geha Mental Health Center during the study period were analyzed. Of them, 743 have been diagnosed with schizophrenia (Sz), 170 with schizoaffective disorder (SzA), and 158 with bipolar disorder (BP-I). Baseline sCK and PANSS values were obtained from each patient upon admission. Our results show that LnsCK is higher in patients with BP-I in comparison with patients with SZ, but not significantly different compared to patients with SzA. A multivariate analysis using linear regression model in which LnsCK was predicted by factors such as PANSS-total and sub-scores, IM injection, BMI, gender, and age among patients at each admission, revealed that PANSS-depression was inversely associated with LnsCK level in SzA and BP-I and not in SZ. A positive association was found between PANSS-total and sCK in SzA and BP-I; however, PANSS-positive scores correlated with sCK only in SzA. After controlling for confounders, it seems that sCK level is associated with the both affective and psychotic components. Serum CK may serve as a biomarker for affective exacerbation rather than psychosis.

1. Introduction

Creatine kinases (CK) are enzymes found throughout the body, yet exist predominantly in a cell type-dependent manner in tissues with high energy demands and large fluctuations in energy metabolism such as muscles and nerves. More specifically, CK enzymes are expressed as two isoenzymes in mitochondrial CK-ubiqitious and CK-sarcomeric isoforms, and as three cytosolic isoforms (mono or dimeric): CK-MM, CK-MB, and CK-BB are most prevalent in skeletal muscles, heart, and brain respectively (Wallimann et al., 1992).

It has been previously shown that the total amount of CK in serum (sCK) is primarily of the cytosolic CK-MM isoform, as CK-BB does not naturally cross the blood brain barrier or switch isotype form Meltzer (1976) and Wallimann et al. (1992). Under normal physiological conditions, total CK levels vary depending on age, gender, race, muscle mass, physical activity and climatic condition (Brancaccio et al., 2008). Baseline levels of sCK tend to be persistently higher in males than females (Manor et al., 1998), in black males compared to caucasian males, and in those with higher body mass (Black et al., 1986; Brancaccio et al., 2008). Noteworthy, higher levels of plasma or sCK are found in both black females and males (Meltzer and Holy, 1974). The upper limit for normal sCK has been established to less than 150 U/L for women and less than 175 U/L for men (CK NAC UV, 1996).

Moreover, there are many known factors associated with increased levels of sCK such as psychomotor agitation, medications, drugs, intramuscular injections (IM injections), rhabdomyolysis, and myocarditis (Swartz and Breen, 1990; Knochel, 1993; APA, 1994). An increase in sCK-MM is thought to be a hallmark of muscle injury (Knochel, 1993; APA, 1994), and more specifically, in conditions that affect the muscle fiber itself (Meltzer, 1976; Lott and Landesman, 1984). An increase in serum CK-MM has been found in patients with acute diseases of the brain, such as infections, vascular disease, and trauma (Meltzer, 1976). High levels of sCK typically last for 1–2 weeks, with maximum levels reaching 20,000 IU/L (Meltzer, 1969). Therefore, any study that links sCK and clinical phenomenon should take these factors into account.

Previous research has also demonstrated variable, but consistent, high levels of sCK in the majority of patients undergoing acute psychoses (Meltzer, 1976; Meltzer et al., 1980; Hatta et al., 1998; Manor et al., 1999; Hermesh et al., 2001). One of the earliest

* Correspondence to: 1 Helsinki St., P.O. Box 102, Petach-Tikva 49100, Israel.
E-mail address: shollander@ucdavis.edu (S. Hollander).

http://dx.doi.org/10.1016/j.psychres.2016.01.058
0165-1781/

and well-known clinical reports of schizophrenia was the occurrence of psychosis-associated creatine kinase-emia (PACK), which refers to marked levels of sCK upon episodes of acute psychosis (Meltzer, 1968, 1969, 1970, 1973, 1976; Coffey et al., 1970; Schweid et al., 1972; Gosling et al., 1972; Martin et al., 1972; Faulstich et al., 1984; Hermesh et al., 2002). Increased sCK levels are found in the majority of hospitalized patients with acute schizophrenia and patients with affective psychoses (Meltzer, 1976). Hermesh et al. found that patients, mostly with schizophrenia, exhibit consistently elevated sCK levels during each successive psychotic episode, and suggested patients who exhibit marked levels of sCK during acute psychosis are at higher risk for neuroleptic malignant syndrome (NMS) (Spivak et al., 1990; Hermesh et al., 2002).

Surprisingly, sCK levels can exceed up to 100× the normal value during psychotic exacerbations; however, this regularly does not indicate myonecrosis (i.e. rhabdomyloysis) (Meltzer, 1969; Meltzer and Moline, 1970; Hermesh et al., 2001). Patients who demonstrated high sCK during acute psychosis also demonstrate persistently moderately increased levels of sCK during non-psychotic periods (Meltzer, 1976).

Previous studies have investigated the relationship between sCK and psychosis, however yielding variable and inconsistent results. Often times, study samples were very small, and potentially confounded by variables known to play a contributing role to levels of sCK; excitability was not adjusted for in previous studies as well. Furthermore, many of these studies have been published over three decades; therefore, it is timely to conduct a well-controlled study regarding sCK and psychosis. We sought to further investigate this relationship while adjusting for variables that affect sCK expression. To our knowledge, this is the first study to examine this relationship using a large sample size of psychiatric inpatients.

2. Methods

2.1. Subjects

In this retrospective study, we obtained a sample size of 1054 hospitalized patients from Geha Mental Health Center (GMHC) – a large regional university affiliated psychiatric hospital in Petach Tikva, Israel, covering a catchment area with a population of 800,000 people. Data was retrieved from electronic medical records of patients hospitalized during 2008–2014 (study period). We established the inclusion criteria as follows: men and women above 18 years of age, hospitalization in GMHC within study period, record of sCK and PANSS at admission, unmedicated, and diagnosis of schizophrenia (Sz), schizoaffective disorder (SzA) or bipolar disorder-I (BP-I) using DSM-IV-TR diagnostic criteria (APA, 1994).

Standard baseline sCK values along with routine blood draw were obtained from each newly admitted patient within 24 hours from admission which is part of the routine laboratory workup for all new patients admitted to GMHC. CK serum levels were evaluated by the CK NAC UV liquid (1996) – a UV Kinetic determination of CK in serum and plasma (CK NAC UV, 1996). The upper limit for normal sCK was established to less than 150 U/L for women and less than 175 U/L for men (CK NAC UV, 1996). The isotype of CK in serum was not determined.

Routine Positive and Negative Syndrome Scale (PANSS) was filled within the first 3 days of admission by a trained rater. PANSS was validated to measure the positive and negative symptoms of schizophrenia, and assess general psychopathology (Montoya et al., 2011). In our study, PANSS was measured as a total (PANSS-T); subscales were calculated for depression (PANSS-D) and psychosis (PANSS-P). A subscale for agitation, excited component (PANSS-EC), was measured by poor impulse control, tension, hostility, uncooperativeness, and excitement (Kay et al., 1987).

Demographic variables that were collected via medical records included age, gender, and clinical variables such as length of hospitalization, medications at admission, body mass index (BMI), short-acting intramuscular injection (IM injection) administered upon admission, metabolic indexes, hemodynamic indexes, and other blood laboratory tests such as albumin, platelet count and WBCs as measures of acute-phase response.

2.2. Statistical analyses

We used SPSS version 20 for statistical analyses. Study population was divided according to diagnosis (i.e. schizophrenia, schizoaffective disorder, and bipolar disorder). In order to obtain a normal distribution of sCK levels, a natural logarithmic (Ln) transformation of individual sCK levels (LnsCK) was performed. We conducted a univariate comparison for factors that are related to LnsCK level differences using one-way analysis of variance (ANOVA) for continuous variables and χ^2 for categorical variables. We compared LnsCK across diagnoses using one-way ANOVA, followed by Tukey's post hoc test. Data are expressed when the F value was significant, as mean and standard deviation. Next, we performed within each diagnosis a univariate and multi-variate analysis to evaluate the associations between LnsCK levels across demographic and clinical characteristics. We performed a multi-variate analysis using a multiple linear regression models in which LnsCK was predicted by several relevant factors. Significance was considered when $p < 0.05$.

3. Results

Our study sample consisted of 1054 patients hospitalized in GMHC at least once during the study period, and had PANSS and sCK measurements upon admission. Of them, 743 have been diagnosed with Sz, 170 with SzA, and 158 with BP-I. Demographic, clinical and laboratory data of all subjects are presented in Table 1. It is of note that although there was no significant difference across diagnoses in mean level of sCK, it was higher than the normal value (upper limit150 U/L for women, 175 U/L for men) in all three diagnoses (Table 1) (CK NAC UV, 1996). Out of the Sz, SzA and BP-I 44.2%, 49.4% and 58.2 %, respectively, were above the normal value.

A one-way ANOVA was performed to determine whether group differences exist between multiple parameters. PANSS-P score was statistically significant between groups, $F(2,1051)=5.43$, $p < 0.005$, as well as PANSS-Total, $F(2,1051)=23.27$, $p < 0.0005$. Additionally, LnsCK differed significantly between groups $F(2, 1051)=4.94$, $p < 0.005$. Tukey post-hoc analysis revealed that LnsCK levels in patients with BP-I are significantly higher ($p=0.01$) than patients with Sz, but did not differ significantly from patients with SzA ($p=0.66$).

A *t*-test analysis was conducted between gender, IM injections at admission, compulsory stay and LnsCK. As expected, there was a statistically significant between-gender difference in LnsCK (5.46 ± 1.1 for males vs. 4.92 ± 1.1 for females, $t=7.5$, $df=1,052$, $p < 0.0001$). No statistical difference was found in LnsCK levels between patients who were administered IM injections at admission compared to those without injections (5.44 ± 1.10 vs. 5.25 ± 1.2, respectively; $t=-1.5$, $df=1052$, $p=0.12$). LnsCK levels were greater ($p < 0.005$ for all) in patients admitted under civil commitment compared to the other legal status at admission (civil commitment 5.52 ± 1.2, criminal commitment 5.05 ± 1 and consent 5.1 ± 1; ANOVA:$F=13.9$, $p < 0.0001$).

A statistically significant correlation was found between LnsCK levels and pulse ($r=0.14$, $p < 0.0001$), WBCs ($r=0.10$, $p < 0.001$), albumin ($r=-0.06$, $p=0.03$), and weight ($r=0.13$, $p < 0.0001$) and was not found between systolic blood pressure, platelet count, C-reactive protein (CRP) values and temperature.

Association between LnsCK values and PANSS total and subscores are depicted in Table 2. It can be seen that initially the PANSS-P sub-score was positively associated with LnsCK; however, significance was lost following adjustment to covariates.

Fig. 1 visually illustrates the linear correlations between LnsCK and PANSS-T, PANSS-P, and PANSS-D based on a multiple linear regression models, adjusting for gender, BMI, intramuscular injection, and excitability that may affect LnsCK across diagnoses. It is shown that there is a significant relationship between LnsCK and PANSS-D in patients with SzA and BP-I.

4. Discussion

In this present study, we investigated the correlation between sCK levels at admission across patients with schizophrenia,