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Relationship between post-traumatic stress disorder - and oxidative stress - a PubMed approach

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Abstract
Introduction. Post-traumatic stress disorder (PTSD) is a severe anxiety syndrome and oxidative stress may be involved.
Aims. The objective was to highlight the relationship between PTSD and oxidative stress, in an approach from the PubMed perspective publication
Methods. Keywords were selected: PTSD, PTSD and Oxidative stress (PTSD+OS), PTSD and malondialdehyde (PTSD+MDA), PTSD and reactive oxygen species (PTSD+ROS). The PubMed filter chosen was: a) gender (Sex), with sub-filters: male (HM), female (HF), male and female (HM+HF); b) Age with sub-filters: 0-18, 19-44, 45-64, >65 and >80 years. Analysis criteria: total number of publication (N); the average number of publications per year (N/Y).
Results. Of the keywords referring to OS, the highest N and N / Y was for PTSD+OS. For PTSD+MDA and PTSD+ROS, N was fluctuating throughout the publication period. For Sex filter, of the key word combinations referring to OS, most publications were for PTDS+OS at M+F. For Age filter, of the key word combinations referring to OS, most publications were for PTSD+OS at 19-44.
Conclusions. 1) Studies on PTSD and Oxidative Stress are very much fewer compared to those for PTSD, but their presence proves interesting in the research in this direction. 2) Among the keyword combinations referring to oxidative stress, those about PTSD + ROS were more numerous than those for PTSD + MDA, both in terms of publication period and total number of publications, which proves a greater concern for research. regarding ROS. 3) All keyword combinations were preferred in the research, being subjects of both genders and age between 19-44 years, which shows an interest for mature adult subjects. 4) Although studies on the relationship between PTSD and oxidative stress are still numerically low, their number is important, proving a growing interest over time in this field of research.
Keywords: PTSD, Oxidative stress, malondialdehyde, reactive oxygen species, PubMed.

Introduction

Traumatic life events, including earthquakes, war, and interpersonal conflict, cause a cascade of psychological and biological changes known as post-traumatic stress disorder (PTSD) (Atli et al., 2016). Post-traumatic stress disorder (PTSD) is a serious condition (***, 2000), a severe anxiety syndrome that is diagnosed on the basis of basic clinical symptoms for a period of more than one month (Tylee et al., 2014). The type and severity of trauma are important factors of PTSD (Yehuda, 2009). There are a variety of structural and functional changes in the brain in the pathogenesis of PTSD and oxidative stress may be involved (Michels et al., 2014).

On the other hand, oxidative stress is due to increased production of reactive oxygen species or reduced enzymatic or non-enzymatic antioxidant factors (Hovatta et., 2010), therefore due to the oxidant / antioxidant imbalance (Ceprnja et al., 2011). Thus, in oxidative stress an increasing amount of reactive oxygen species (ROS) and / or reduced antioxidant defense mechanisms occurs (Serafini & Del Rio, 2006). Increased production of reactive oxygen species causes destruction of all major classes of macromolecules, resulting in, among others, mitochondrial dysfunction (Hovatta et., 2010).

In the pathogenesis of PTSD, oxidative stress plays an important role (Ozdemir et al., 2015). It has been found that there is a greater impact of PTSD development on oxidative markers than trauma itself (Atli et al., 2016).

A study that investigated 12 PTSD participants and 17 non-PTSD participants showed significantly higher levels of γ-amino butyric acid (GABA) and glutathione (a marker for neuronal oxidative stress) in PTSD participants (Michels et al., 2014). For 74 male active soldiers in the

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Croatian Armed Forces from 1991 to 1995 (46 with chronic and current PTSD, 28 healthy subjects), carbonyl protein concentrations were significantly lower in the PTSD group than in the control group (Ceprnja et al., 2011). For male war veterans who actively participated in the war in their homeland, Croatia, and who had post-traumatic stress disorder, the values of catalytic concentrations of erythrocyte superoxide dismutase and erythrocyte glutathione peroxidase were significantly lower ($P < 0.001$) (Borovac et al., 2015). In adult attention deficit hyperactivity disorder (A-ADHD), MDA levels have been increased, indicating increased oxidative stress in this disease (Bulut et al, 2007). Also, in some neuropsychiatric disorders, such as depression, free radicals and their derivatives play an important role (Gałecki et al., 2009). Serum malondialdehyde (MDA) levels and paraoxonase (PON1) enzyme activity may serve as biochemical markers of PTSD diagnosis (Atli et al., 2016). Malondialdehyde (MDA) is a biomarker of oxidative stress in many health problems, including mood disorders (Popović et al., 2019).

Hypothesis

So far, studies have shown interest in PTSD in general. On the other hand, the relation between PTSD and oxidative stress relationship remains relatively little analyzed, as evidenced by the number of publications found in the PubMed database.

Objectives

The objective was to highlight the relationship between PTSD and oxidative stress, based on a search of the PubMed publications.

Material and methods

The obtained information was from the PubMed database.

Keywords

PTSD is known to be one of the most important contexts that trigger oxidative stress.

To highlight the relationship between PTSD and oxidative stress, we selected for analysis key words that relate to the assessment of stress: malondialdehyde and reactive oxygen species, as markers of oxidative stress. For the analysis of oxidative stress, in the context of PTSD, several combinations of specific keywords were selected:

a) posttraumatic stress disorders (PTSD);

b) posttraumatic stress disorders AND oxidative stress (PTSD+OS);

c) posttraumatic stress disorders AND malondialdehyde (PTSD+MDA);

d) posttraumatic stress disorders AND reactive oxygen species (PTSD+ROS).

PubMed filters

The PubMed filters we chose for the analysis were: Sex and Age, each of these filters forming a study group. Within each filter checked, several sub-filters were analyzed:

- For the "Sex" filter, the selected sub-filters were: male (M), female (F), male+female (M+F).

- For the "Age" filter, the selected sub-filters were: 0-18 years, 19-44 years, 45-64 years, >65 years, >80 years.

Periods of research

For a complete evaluation of the total number of publications related to the studied subject, we chose the time periods starting with the year of the first publication announced by the PubMed website and until the end of 2018. It was calculated to the average number of publications per year. We note that this study was started in May 2019 and was completed in September 2019.

Study design

The design was based on the following criteria:

- Analysis of the chosen keywords, in relation to the total number of publication (N).

- Analysis of the chosen keywords, in relation to the sub-filters and the average number of publication per year (N/Y).

Results

For all groups, data distribution was normal, according to the Kolmogorov-Smirnov test. The analysis was made on the chosen time periods.

1. Analysis of selected keywords, referring to N and N / Y (Table I)

The first time it was published was the earliest for PTSD (1964) and the most recent for MDA (2014). The longest publication period was for PTSD (54), and the shortest for PTSD+MDA (2). Of the keywords referring to OS, the highest N and N / Y was for PTSD+OS (N = 84, N /Y=6.4), and the lowest for PTSD+MDA (N = 10, N / Y = 0.6). Among the OS markers, most publications were for PTSD+ROS (N = 15, N / Y = 1).

2. Dynamic analysis of N, for Keyword combinations related to OS (Fig. 1)

For PTSD+OS, in the period 2005-2012 N was fluctuating, in 2006 and 2010 there was no publication and N started to increase since 2013, being the highest in 2018 (14). For PTSD+MDA, N was fluctuating throughout the publication period, being the highest in 2018 (3). For PTSD+ROS, N was fluctuating throughout the publication period, being the highest in 2016 (5).

Table I

Analysis of selected keywords, referring to N and N / Y.

Indicator	Publication period	No years	Total number of publications N	No. Public / year N/Y
PTSD	1964-2018	54	35975	666.2
PTSD+OS	2005-2018	13	84	6.4
PTSD+MDA	2014-2018	4	10	0.6
PTSD+ROS	2004-2018	14	15	1

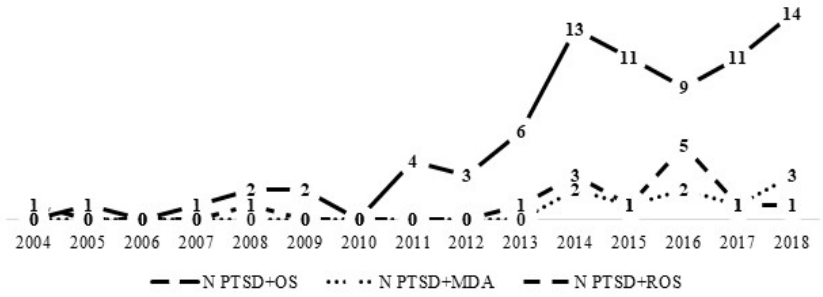

Fig. 1 – Dynamic analysis of N, for Keyword combinations related to OS.

3. Analysis for the Sex filter (Table II)

For all chosen keywords N for M was greater than N for F. For PTSD+OS, N was almost equal for M (51) and M+F (52). Of the keywords combinations referring to OS, most publications were for PTDS+OS at M+F (52) and the fewest for PTSD+MDA at F (3). In the case of PTSD+MDA and PTSD+ROS, N for M+F was equal (12).

Table II
Total publications for keywords related to oxidative stress, reported to the Sex filter.

Indicator	N	M	F	M+F
PTSD	35975	21659	21376	43035
PTSD+OS	84	51	19	52
PTSD+MDA	10	9	3	12
PTSD+ORS	15	8	4	12

4. Analysis for the Age filter (Table III)

Of all the chosen keywords, N for the 19-44 age range was the highest. Of the keywords combinations referring to OS, most publications were for PTSD+OS at 19-44 (21). There was no publication for PTSD+MDA at > 65 years and for PTSD+MDA and PTSD+ROS at > 80 years. In the case of PTSD+MDA and PTSD+ROS, N was equal to 0-18 (1) and 45-64 (3).

Table III
Total number of publications for keywords related to oxidative stress, relative to the Age filter.

Indicator	N	0-18	19-44	45-64	>65	>80
PTSD	35975	10614	18387	12075	4845	1268
PTSD+OS	84	6	21	15	1	1
PTSD+MDA	10	1	5	3	0	0
PTSD+ROS	15	1	3	3	1	0

Discussion

The present paper is a continuation of our concerns about oxidative stress and the MDA marker. (Jurcău et al., 2011; Jurcău & Jurcău, 2013; Jurcău & Jurcău, 2017).

A. Analysis of keywords

An analysis was performed for the number of publications displayed on the PubMed site, analyzing the values on filters and sub filters, for PTSD, regarding oxidative stress (OS, MDA, ROS), using the keywords PTSD, PTSD+OS, PTSD+MDA, PTSD+ROS. Totally, for a period of about 14 years and 4 years respectively, few publications were found for PTSD+ROS (15) and PTSD+MDA (10).

In the case of PTSD+OS, the publishing rate had an increasing trend since the beginning of the publications, proving a growing interest in time for this combination of keywords. Instead, for PTSD+MDA and PTSD+OS, the publishing rate has been fluctuating, which may illustrate an inconsistent interest in studies on these keywords combinations.

B. Analysis of filters

Sex filter

Compared to the male (M), female (F) sub-filters: for all keywords, the number of publications including studies on men was generally higher than the ones that included women. For all keywords, the number of publications with male+female (M+F) subjects were generally more numerous than with male (M) or female (F), proving the interest of publications for both genders.

Age filter

For all chosen keywords combinations, the most numerous publications were for the 19-44 age, which shows the high interest for this age category. Although the interest for the age range 19-44 years is the highest, there are publication interests also for ages 0-18, 45-64 and >65 years. For the 45-64 age group, the publication interest was higher than for 0-18 and >65. Also, for all the chosen keywords, for the age >80 years, the number of publications was generally the lowest or even without studies over the entire time period analyzed, proving a low interest in research on this age.

C. PubMed chronological evidence

PTSD - Oxidative Stress Mechanism

There is a relationship between severe life stress (SLS) and mental illness; "post-traumatic stress disorder" (PTSD) are the most studied mental disorders induced by SLS; PTSD may be due to physical, emotional, or sexual abuse (Fullerton et al., 2004). The main axis involved in stress is the hypothalamic-pituitary-adrenal axis (HPA) (Dedovic et al., 2009), and prolonged glucocorticoid secretion normally reflects a state of chronic stress. In addition, glucocorticoids have a significant effect of inducing oxidative stress, which could be an additional mechanism underlying the increases in disease susceptibility and decreased health observed in chronic stress (Costantini et

al., 2011). It has been shown that there is a link between the HPA axis and oxidative stress, oxidative stress being involved in the stress response: severe life stress (SLS) can directly alter the physiological functioning of the HPA axis, leading to increased ROS production by mitochondria and NADPH. oxidase (Schiavone et al., 2013).

Oxidative Stress Evaluation

In earthquake survivors with PTSD, compared to controls exposed to earthquakes, high levels of serum lipid peroxidation and depleted antioxidant enzymes were observed (Ernster & Dallner, 1995). Exhausted levels of both blood antioxidants, SOD and glutathione transferase were found in Croatian war veterans with PTSD compared to controls (Beal, 2002). During oxidative stress, active oxygen can cause significant damage and can alter the physiological functions of DNA, proteins, enzymes and lipids (Ceprnja et al., 2011). A possible involvement of OXS-related biology in PTSD was found among veterans: significant genome-wide association between a single nucleotide polymorphism (SNP) in the alpha gene of the orphan retinoic acid receptor (RORA; rs8042149) and a diagnosis of PTSD (Wilson et al., 2013). There are preliminary studies indicating the existence of increased oxidative stress in PTSD, which leads to excessive levels of free radicals (Michels et al., 2014). In patients with post-traumatic stress disorder, lower catalytic concentrations of erythrocyte superoxide dismutase and erythrocyte glutathione peroxidase were found, indicating a weaker response to oxidative stress (Borovac et al., 2015).

ROS

In patients with PTSD who witnessed a catastrophic disaster, similar changes were found in the antioxidant transcription of the RNA gene: regulation in the down expression of the antioxidant genes SOD and thioredoxin reductase (which interact with glutathione to detoxify ROS) (Berk, 2009). In depression, the inflammatory process is one of the sources of reactive oxygen species (ROS) (Gałecki et al., 2009a). Oxidative stress consists of an imbalance between the amount of reactive oxygen species (ROS), the main cause of oxidative stress produced by mitochondria and the ability of antioxidant systems to neutralize them (Schiavone et al., 2013). Increased ROS production in the glands corresponding to the HPA axis is associated with the activation of a stress response system in several stress patterns, including social isolation and inflammatory and infectious diseases (Prevatto et al., 2017).

MDA

MDA levels were significantly higher in patients with attention deficit hyperactivity disorder in adults than in control subjects and were correlated with the overall hyperactivity / impulsivity score (Bulut et al, 2007). Antioxidant enzymes such as copper-zinc superoxide dismutase (SOD1), catalase (CAT) and malondialdehyde (MDA) had significantly higher levels of activity, while total plasma antioxidant status was decreased in patients with acute depressive episodes. compared to healthy people (Gałecki et al., 2009b). It was a significant decrease in GPx-1 and SOD-1 activities and increased concentrations of MDA in depressed patients compared to controls (Rybka et al., 2013). MDA is a reliable marker of lipid peroxidation, and PON1 is a known antioxidant enzyme (Atli et al., 2016). In patients with PTSD who survived the earthquake, the activity of the enzyme PON1 was significantly lower and the mean level of MDA was significantly higher than that of the healthy control group ($p < 0.01$ for both measurements), even and differences between these groups did not reach a statistically significant level (Atli et al., 2016).

Conclusions

1. Studies on PTSD and Oxidative Stress are numerically reduced compared to those for PTSD, but their presence proves interest in research in this direction.

2. Among the keyword combinations referring to oxidative stress, those about PTSD + ROS were more numerous than those for PTSD + MDA, both in terms of publication period and total number of publications, which proves a greater concern for research. regarding ROS.

3. For all keyword combinations the preferred research was on subjects of both genders and age between 19-44 years, which shows an interest for mature adult subjects.

4. Although studies on the relationship between PTSD and oxidative stress are still numerically low, their number is important, proving a growing interest over time in this field of research.

Conflicts of interest

Nothing to declare.

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