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Post-traumatic stress disorders after severe sespis or septic shock

Transtornos de estresse pós-traumático após sepse grave ou choque séptico

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ABSTRACT: Post Traumatic Stress Disorder (PTSD) is a medical condition characterized by symptoms of anxiety and depression occurring in people who have a history of traumatic events. This disorder was initially diagnosed in patients that have been exposed to violent events, such as rape or war. Recently, however, PTSD has been also recognized in patients that survived after intensive care unit (ICU) stay. This phenomenon seems to be related to dysfunction of the hypothalamus-pituitary-adrenal axis (HPA) observed in patients treated in ICUs. Since it is known that severe sepsis and septic shock may lead to a situation called critical illness-related corticosteroid insufficiency (CIRCI), we hypothesized that PTSD development after severe sepsis could also be related to HPA dysfunction during sepsis treatment. We performed a literature search, using different databases and diverse combinations of the terms PTSD, sepsis and HPA. Fifteen articles were retrieved and only three filled all the requisites. These three publications were reviewed here. We conclude that the available data are not sufficient to confirm a direct relationship between a sepsis-related hypothalamic-pituitary-adrenal axis dysfunction and the development of post-traumatic stress disorder. Although there is concrete evidence about the existence of this correlation, the published articles represent the work of just one research group, include few patients and did not take into consideration the effect of the intensive care stay in their conclusions.

KEYWORDS: Intensive care unit; Stress disorders, post-traumatic; Hydrocortisone; Critical illness; Hypothalamus; Depression; Anxiety; Sleep disorders.

RESUMO: Transtorno de Estresse Pós-Traumático (TEPT) é uma condição médica caracterizada por sintomas de ansiedade e depressão que ocorrem em pessoas que têm uma história de eventos traumáticos. Esta doença foi inicialmente diagnosticada em pacientes que tenham sido expostos a eventos violentos, como estupro ou guerra. Recentemente, no entanto, o TEPT tem sido também reconhecido em pacientes que sobreviveram após internação na unidade de terapia intensiva (UTI). Esse fenômeno parece estar relacionado a uma disfunção do eixo hipotálamo-pituitária-adrenal (HPA) observada em pacientes tratados em UTIs. Uma vez que é sabido que a sepse grave e o choque séptico podem levar a uma situação chamada insuficiência de corticosteroides relacionado a doença crítica (CIRCI), formulou-se a hipótese de que o desenvolvimento de PTSD após sepse grave também pode estar relacionado a uma disfunção do eixo HPA durante o tratamento da sepse. Foi realizada uma pesquisa bibliográfica, utilizando-se diferentes bases de dados e diversas combinações dos termos PTSD, sepse e HPA. Quinze artigos foram recuperados e apenas três preencheram todos os requisitos. Estas três publicações foram revistas aqui. Conclui-se que os dados disponíveis não são suficientes para confirmar uma relação direta entre a disfunção do eixo hipotálamo-hipófise-adrenal relacionada à sepse e ao desenvolvimento do transtorno de estresse pós-traumático. Embora haja provas concretas sobre a existência dessa correlação, os artigos publicados representam o trabalho de apenas um grupo de pesquisa, incluem poucos pacientes e não levam em consideração o efeito da internação na UTI em suas conclusões.

DESCRITORES: Unidades de terapia intensiva; Transtornos de estresse pós-traumático; Hidrocortisona; Estado terminal; Hipotálamo; Ansiedade; Transtornos do sono.

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INTRODUCTION

Post-traumatic stress disorder

Post-Traumatic Stress Disorder (PTSD) was recognized as a medical entity almost half a century ago, initially in Vietnam War veterans that presented symptoms of depression and anxiety[1]. Later, this diagnosis was applied also to survivors of rape, assault or other violent traumatic events[2].

Nowadays, DSM-5 established some criteria for the diagnosis, divided in clusters[3]:

- History of traumatic event;
- Intrusion: recurrent, involuntary, and intrusive memories; unpleasant nightmares;
- Avoidance: persistent effortful avoidance of distressing trauma-related stimuli after the event;
- Negative alterations in cognition and mood: persistent distorted blame of self or others for causing the traumatic event or for resulting consequences and persistent negative trauma-related emotions;
- Alterations in arousal and reactivity: irritable or aggressive behavior, self-destructive or reckless behavior, problems in concentration, sleep disturbance;
- Persistence of symptoms for more than one month.

In more recent years, some authors noticed that patients that survived after being treated for severe illnesses in Intensive Care Units (ICUs) presented later with symptoms that resemble the ones described by patients diagnosed with PTSD[4,5].

PTSD etiology is still not completely understood, and several factors seem to affect the outcome of the disease, including genetic variations[6] (Wang et al. 2011) and trauma intensity[7]. Among the main mechanisms described to explain the development of PTSD, the dysfunction of the hypothalamic-pituitary-adrenocortical (HPA) axis seems to be one of the most important[8]. Nevertheless, this relationship between PTSD and HPA has been described mainly in post violent traumatic events and no consensus exists regarding the role of this mechanism in PTSD after ICU treatment.

Intensive care and sepsis

Sepsis is the most common diagnosis in ICUs around the world[9], including Brazil[10]. Severe sepsis and septic shock develop when the initial appropriate response of the host to a bacterial or fungal infection becomes amplified, and then deregulated[11]. Clinically, the onset is insidious, with fever, mental confusion, urinary and hematological changes. The patient may then develop respiratory and / or renal failure, coagulation disorders and hypotension unresponsive to treatment[12]. The mortality in these cases, worldwide, is about 30-50%[13,14], similar to the data in the Intensive Care Unit of our service.

Sepsis pathophysiology is the result of complex interactions between the host immune system and the invading pathogens. One interesting point in this phenomenon is the role played by the HPA axis. There is a relative adrenal insufficiency in critically ill patients is approximately 20%, with an incidence as high as 60% in patients with severe sepsis and septic shock[15]. The mechanisms leading to inadequate cortisol production during critical illness are complex, poorly understood, and likely include decreased production of CRH, ACTH, and cortisol[16], as described below.

From the studies described above, it seems clear that PTSD and critical illness, particularly severe sepssis and septic shock, share a common pathophysiologic mechanism, that is, a marked dysfunction of the HPA axis. Therefore, in order to better understand this relationship, it is necessary to detail the HPA axis, in health and disease.

The hypothalamus-pitutitary-adrecortical axis

Cortisol (hydrocortisone) is the major endogenous glucocorticoid secreted by the adrenal cortex. Cholesterol is the principal precursor for steroid biosynthesis; at rest and during stress, approximately 80% of circulating cortisol is derived from plasma cholesterol, with the remaining 20% being synthesized in situ from acetate and other precursors[17]. The adrenal gland does not store cortisol; increased secretion arises due to increased synthesis under the control of adrenocorticotrophic hormone (ACTH) by the anterior pituitary gland which, by itself, is stimulated by corticotropin-releasing hormone (CRH), released by paraventricular nucleus of the hypothalamus[16]. This part of the hypothalamus is sensitive to adrenal needs and is the responsible for triggering the whole process of cortisol secretion.

Once secreted, over 90% of circulating cortisol is bound to corticosteroid-binding globulin (CBG) with 10% in the free, biologically active form[18]. The circulating half-life of cortisol varies from 70 to 120 min, with a biological half-life of approximately 6 to 8 h.

Further, in order to exert its effects, cortisol binds to specific receptors on the cell nuclei, the glucocrticoid receptors, or GRs[19]. Two isoforms of the GR have been isolated, namely GR-α and GR-β. The GR-β isoform fails to bind cortisol and activate gene expression, and thus, functions as a negative inhibitor of GR-α[19], adding another complexity level to the process.

During the past decade, it was recognized that many critically ill patients present a corticosteroid deficiency,

even though their cortisol secretion was in the normal range. The term Critical Illness-Related Corticosteroid Insufficiency (CIRCI) was then coined to describe this clinical entity[16] (Marik 2009).

PTSD, sepsis and the HPA axis

Considering that:

- it is well known that during sepsis a marked dysfunction of the HPA axis is observed;
- patients treated in ICUs present higher incidence of posttraumatic stress disorder;
- it has been described that there is a direct correlation of the development of PTSD and dysfunction of HPA axis;
- our main objective in this study is to determine whether there is a higher incidence of PTSD in patients that survived from severe sepsis or septic shock and the role of exogenous corticosteroid administration in this phenomenon.

METHODOLOGY

The literature search was conducted using computerized databases including PUBMED, SciELO and LILACS, regardless the time the articles were published. Our main search strategy consisted of the following keywords: "posttraumatic stress disorder" AND "sepsis" AND "cortisol". The term "post-traumatic stress disorder" was also substituted by "PTSD"; the term "sepsis" was also sought as "septic shock"; the term "cortisol" was also researched as "corticosteroids", "hypothalamic-pituitary-adrenocortical axis" or "HPA axis". Abstracts were read thoroughly before complete articles were obtained and the references from the relevant publications were manually explored to ascertain further potential articles. The search was restricted to studies that were published in English or in Portuguese. Observational studies and retrospective analysis were not eliminated. Case reports/case series and review were not considered.

RESULTS

Based on the initial search results, 15 titles and abstract were examined. One additional publication was retrieved by hand search of the references. Twelve articles were excluded, since they did not present any data related to the main focus of our work. Most of these articles refer to PTSD and critical care units, with no particular interest in sepsis. One study was not considered because it was a review written by the same authors of other studies. In the end, only three studies were reviewed that contain the relationship between sepsis, the HPA axis and further development of PTSD.

The first article to explore this relationship was written in 1999, by Schelling et al.[20]. In this study, authors used a retrospective case-controlled analysis of 27 patients who received standard septic-shock treatment and compared them to another septic shock group, with the same number of patients that received supplemental hydrocortisone in doses equivalent to the maximal endocrine secretion rate. Medical records after ICU discharge were scanned in order to find the prevalence of PTSD. PTSD was diagnosed using the Posttraumatic Stress Syndrome-10 question inventory and quality of life measured with the Medical Outcomes Study Short Form Survey. The result of the study was that hydrocortisone treatment during septic shock significantly lowered the incidence of PSTD (as only 5 of the 27 patients of the group developed PTSD in contrast to the protocol-driven control group in which 16 of the 27 did) and could improve the quality of life, long after the ICU discharge, in patients who were treated for severe sepsis or septic shock.

Further, in 2001, the same group published another study using a different approach[21]. This time authors recruited patients (n=20) from an on going prospective, randomized double-blind study on the hemodynamic effects of hydrocortisone during septic shock. Eleven patients had received placebo and nine stress doses of hydrocortisone. Posttraumatic stress disorder was diagnosed 31 months (median) after intensive care unit discharge using specific tests based on the DSM-IV criteria. Furthermore, the number of categories of traumatic memory from ICU treatment was determined in both groups at that time. Confirming the results presented in their previous study, only one of nine patients from the hydrocortisone group developed posttraumatic stress disorder, compared with seven of 11 patients in the placebo group ($p=0.02$). There was no significant difference with regard to the number of categories of traumatic memory between the hydrocortisone and placebo groups. Their conclusion was that the administration of hydrocortisone during septic shock in a dosage similar to the endogenous maximal production rate was associated with a lower incidence of posttraumatic stress disorder in long-term survivors, which seems to be independent of the number of categories of traumatic memory.

Finally, in 2006, another study was published, where the same authors present a new series of cases, with, actually, no new findings[22]. It was a review, with a few new data, confirming their previous findings and introducing to their discussion the new concept of critical illness-related corticosteroid insufficiency (CIRCI). Although no new information was provided in this study, their discussion is more extensive. They list studies which point to a relationship between the HPA axis, glucocorticoid

signaling, ICU patients and development of PTSD. The results indicate that the administration of hydrocortisone to CIRCI patients can bring about many benefits. These include the treatment of CIRCI and its implications, such as the extinction of traumatic memory retrieval from patients. It is necessary to observe here, that their review focused on patients at an ICU, and not in patients with the particular diagnostic of sepsis.

As a conclusion for their three articles, the authors state that regulation of the glucocorticoid signalling is essential for controlling stress or, at least, that administration of exogenous hydrocortisone be involved. They also state that this presents a whole new treatment procedure for ICU patients, who also represent an interesting group for observing the effects of stress hormones and the development of PTSD.

DISCUSSION

There was a limited number of articles focused on the role of critical illness-related corticosteroid insufficiency (CIRCI) or the hypthalamic-pituitary-adrenal (HPA) axis on the development of Post-Traumatic Stress Disorder (PTSD) in patients with severe sepsis or septic shock[20-23]. Interestingly these articles were limited to only one group, from the Ludwig-Maximilians-University, Munich, Germany.

The main difficulty comes from the fact that all patients diagnosed with severe sepsis or septic shock are currently treated in ICUs[24]. As described previously[4,5], it is well known that patients treated in ICUs have a higher chance of developing PTSD. Moreover, this late sequelae may be avoided if patients receive supplemental corticosteroids during their ICU stay[8].

Therefore, in order to know with certainty whether sepsis by itself (and its related CIRCI) are the cause of PTSD, this confounding factor (the ICU stay) should be eliminated. Unfortunately, this is not possible at the present moment, what renders our main question impossible to answer based solely on the current literature

Nevertheless, we can envision series of experiments that could help clarify this issue in the future.

First, we believe that a large number of patients would be necessary to address this subject. The studies reported here were unicentric and enroled a small number of patients[20-23]. We can think of a large sample of ICU patients divided in four groups: Septics receiveng CE, Non-Septics receiving CE, Septics not receiving CE and Non-septics not receiving CE. These patients would be paired for time of ICU, previous diseases, age, and other factors. A thorough statistical analysis could be performed and, if the number of patients is large enough, an answer whether sepsis related CIRCI is the responsible for late PTSD development.

Other approaches involve the development of laboratory and genetic markers of PTSD and their application to the follow-up of septic patients. Although some attempts have been made in this field[25] no marker is already in sue in the clinical set. This kind of approach, however, may be a promising pathway in the near future.

CONCLUSION

The available data are not sufficient to confirm a direct relationship between a sepsis-related hypothalamic-pituitary-adrenal axis dysfunction and the development of prost-traumatic stress disorder. Although there is concrete evidence about the existence of this correlation, the published articles represent the work of just one research group, include few patients and did not take into consideration the effect of the intensive care stay in their conclusions.

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REFERENCES

1. Fairbank JA, Nicholson RA. Theoretical and empirical issues in the treatment of post-traumatic stress disorder in Vietnam veterans. J Clin Psychol. 1987;43(1):44-55. Available from: http://goo.gl/GwSpqi
2. Pompili M, Sher L, Serafini G, Forte A, Innamorati M, Dominici G, Lester D, Amore M, Girardi P. Posttraumatic stress disorder and suicide risk among veterans: a literature review. J Nerv Ment Dis. 2013;201(9):802-12. doi: 10.1097/NMD.0b013e3182a21458.
3. American Psychiatric Association (APA). Diagnostic and statistical manual of mental disorders - DSM-5. Washington, DC; 2013.
4. Jones C, Griffiths RD, Humphris G, Skirrow PM. Memory, delusions, and the development of acute posttraumatic stress disorder-related symptoms after intensive care. Crit Care Med. 2001;29(3):573-80. Available from: http://goo.gl/raA50W
5. Cuthbertson BH, Hull A, Strachan M, Scott J. Post-traumatic stress disorder after critical illness requiring general intensive care. Intensive Care Med. 2004;30(3):450-5. doi: 10.1007/

s00134-003-2004-8

6. Wang Z, Baker DG, Harrer J, Hamner M, Price M, Amstadter A. The relationship between combat-related posttraumatic stress disorder and the 5-HTTLPR/rs25531 polymorphism. Depress Anxiety. 2011;28(12):1067-73. doi: 10.1002/da.20872.
7. Kuo JR, Kaloupek DG, Woodward SH. Amygdala volume in combat-exposed veterans with and without posttraumatic stress disorder: a cross-sectional study. Arch Gen Psychiatry. 2012;69(10):1080-6. doi: 10.1001/archgenpsychiatry.2012.73.
8. Morris MC, Compas BE, Garber J. Relations among posttraumatic stress disorder, comorbid major depression, and HPA function: a systematic review and meta-analysis. Clin Psychol Rev. 2012;32(4):301-15. doi: 10.1016/j.cpr.2012.02.002.
9. Kumar G, Kumar N, Taneja A, Kaleekal T, Tarima S, McGinley E, Jimenez E, Mohan A, Khan RA, Whittle J, Jacobs E, Nanchal R, Milwaukee Initiative in Critical Care Outcomes Research Group of Investigators. Nationwide trends of severe sepsis in the 21st century (2000-2007). Chest. 2011;140(5):1223-31. doi: 10.1378/chest.11-0352.
10. Silva E, Pedro M de A, Sogayar AC, Mohovic T, Silva CL, Janiszewski M, Cal RG, de Sousa EF, Abe TP, de Andrade J, de Matos JD, Rezende E, Assunção M, Avezum A, Rocha PC, de Matos GF, Bento AM, Corrêa AD, Vieira PC, Knobel E; Brazilian Sepsis Epidemiological Study. Brazilian Sepsis Epidemiological Study (BASES study). Crit Care. 2004;8(4):R251-60. doi:10.1186/cc2892.
11. Hotchkiss RS, Karl IE. The pathophysiology and treatment of sepsis. N Engl J Med. 2003;348(2):138-50. doi: 10.1056/NEJMra021333.
12. Dellinger RP, Levy MM, et al. Surviving sepsis campaign: international guidelines for management of severe sepsis and septic shock: 2008. Crit Care Med. 2008;36(1):296-327. doi: 10.1097/01.CCM.0000298158.12101.41.
13. Teles JM, Silva E, Westphal G, Filho RC, Machado FR. Surviving sepsis campaign in Brazil. Shock. 2008;30(Suppl 1):47-52. doi: 10.1097/SHK.0b013e318181a128.
14. Vincent JL, Atalan HK. Epidemiology of severe sepsis in the intensive care unit. Br J Hosp Med (Lond). 2008;69(8):442-3. http://goo.gl/jSHqYa.
15. Annane D, Maxime V, Ibrahim F, Alvarez JC, Abe E, Boudou P. Diagnosis of adrenal insufficiency in severe sepsis and septic shock. Am J Respir Crit Care Med. 2006;174(12):1319-26. doi: 10.1164/rccm.200509-1369OC.
16. Marik PE. Critical illness-related corticosteroid insufficiency. Chest. 2009;135(1):181-93. doi: 10.1378/chest.08-1149.
17. Arlt W, Stewart PM. Adrenal corticosteroid biosynthesis, metabolism, and action. Endocrinol Metab Clin North Am. 2005;34(2):293-313, viii. doi: 10.1016/j.ecl.2005.01.002.
18. Dunn JF, Nisula BC, Rodbard D. Transport of steroid hormones: binding of 21 endogenous steroids to both testosterone-binding globulin and corticosteroid-binding globulin in human plasma. J Clin Endocrinol Metab. 1981;53(1):58-68. doi: http://dx.doi.org/10.1210/jcem-53-1-58.
19. Oakley RH, Jewell CM, Yudt MR, Bofetiado DM, Cidlowski JA. The dominant negative activity of the human glucocorticoid receptor beta isoform. Specificity and mechanisms of action. J Biol Chem. 1999;274(39):27857-66. doi: 10.1074/jbc.274.39.27857.
20. Schelling G, Stoll C, Kapfhammer HP, Rothenhäusler HB, Krauseneck T, Durst K, Haller M, Briegel J. The effect of stress doses of hydrocortisone during septic shock on posttraumatic stress disorder and health-related quality of life in survivors. Crit Care Med. 1999;27(12):2678-83.
21. Schelling G, Briegel J, Roozendaal B, Stoll C, Rothenhäusler HB, Kapfhammer HP. The effect of stress doses of hydrocortisone during septic shock on posttraumatic stress disorder in survivors. Biol Psychiatry. 2001;50(12):978-85. doi: 10.1016/S0006-3223(01)01270-7.
22. Schelling G, Roozendaal B, Krauseneck T, Schmoelz M, De Quervain D, Briegel J. Efficacy of hydrocortisone in preventing posttraumatic stress disorder following critical illness and major surgery. Ann N Y Acad Sci. 2006;1071:46-53. doi: 10.1196/annals.1364.005.
23. Schelling G, Stoll C, Haller M, Briegel J, Manert W, Hummel T, Lenhart A, Heyduck M, Polasek J, Meier M, Preuss U, Bullinger M, Schüffel W, Peter K. Health-related quality of life and posttraumatic stress disorder in survivors of the acute respiratory distress syndrome. Crit Care Med. 1998;26(4):651-9. Available from: http://goo.gl/4gFumF
24. Jones AE, Puskarich MA. The surviving sepsis campaign guidelines 2012: update for emergency physicians. Ann Emerg Med. 2014;63(1):35-47. doi: 10.1016/j.annemergmed.2013.08.004.
25. Battaglia M. Gene-environment interaction in panic disorder and posttraumatic stress disorder. Can J Psychiatry. 2013;58(2):69-75. Available from: http://goo.gl/jPUHbj