Advances in Clinical Medicine 临床医学进展, 2023, 13(3), 3349-3355
Published Online March 2023 in Hans. https://www.hanspub.org/journal/acm
https://doi.org/10.12677/acm.2023.133476

Hans汉斯

多模态监测在脓毒症相关性脑病中的研究进展

幸奠伟，许　峰*

重庆医科大学附属儿童医院重症医学科，重庆

收稿日期：2023年2月8日；录用日期：2023年3月4日；发布日期：2023年3月13日

摘　要

脓毒症相关性脑病(Sepsis Associated Encephalopathy, SAE)是一种弥漫性脑功能障碍，继发于体内感染，却无明显的中枢神经系统感染。SAE急性期以意识和精神状态改变为主要特征，与幸存者的不良预后相关，目前仍缺乏有效的诊断方法。SAE患者病死率及相关并发症的增加会给家庭带来严重的经济负担，而单一的监护方式无法对SAE进行早期的预警及诊断。大脑的多模态监测可从多层面、多角度对脓毒症患者的大脑进行评估，本文拟对脓毒症相关性脑病多模态监测的研究进展进行综述，以提高人们对脓毒症相关性脑病的认识与诊治水平。

关键词

脓毒症，脓毒症相关性脑病，多模态监测

Research Progress of Multimodal Monitoring in Sepsis-Associated Encephalopathy

Dianwei Xing, Feng Xu*

Department of Critical Care Medicine, Children's Hospital Affiliated to Chongqing Medical University, Chongqing

Received: Feb. 8th, 2023; accepted: Mar. 4th, 2023; published: Mar. 13th, 2023

Abstract

Sepsis associated encephaloopathy (SAE) is a diffuse brain dysfunction caused by internal infection and is without central nervous system infection. The acute phase of SAE, characterized by delirium and altered consciousness, is associated with poor prognosis in survivors. There are still

*通讯作者。

文章引用: 幸奠伟, 许峰. 多模态监测在脓毒症相关性脑病中的研究进展[J]. 临床医学进展, 2023, 13(3): 3349-3355.
DOI: 10.12677/acm.2023.133476

few effective diagnostic methods. The increase in case fatality and related complications in patients with SAE may impose a serious financial burden to families, and a single monitoring method cannot provide early warning and diagnosis of SAE. Multimodal monitoring can evaluate the brain of sepsis patients from multiple levels and perspectives, and this article intends to review the research progress of multimodal monitoring of sepsis-related encephalopathy to improve people's understanding, diagnosis and treatment of sepsis-related encephalopathy.

Keywords

Sepsis, Sepsis-Associated Encephalopathy Brain, Multimodality Monitoring

1. 引言

脓毒症是由于宿主对感染的反应失调而引起的危及生命的器官功能障碍[1]。脓毒症相关性脑病(Sepsis Associated Encephalopathy, SAE)是脓毒症常见的并发症之一，它是一种弥漫性脑功能障碍，继发于体内感染，但无明显的中枢神经系统感染证据。SAE 常发生在重症监护室的危重患者中，SAE 急性期意识和精神状态改变为主要特征，具体表现为躁动、幻觉、注意力不集中、睡眠－觉醒周期紊乱、嗜睡和昏迷等[2]。SAE 与脓毒症患者的预后不良和长期认知功能障碍相关，SAE 患者的病死率及相关并发症的增加会给家庭带来严重的经济负担[3] [4]。单一的脑功能监测无法对 SAE 进行早期的预警、诊断及预后评估，大脑的多模态监测已经广泛应用于临床，本文拟从神经影像学成像、神经电生理检查、脑灌注及脑氧饱和度监测、生物标记物检测等方面进行综述，以期望通过早发现、早诊断，可以对 SAE 进行早期有效的治疗。

2. 神经影像学成像

目前 CT 和 MRI 是临床上最常见的头颅成像工具。对于脓毒症患者，当出现局灶性的神经症状或体征时，CT 及 MRI 检查是必要的。然而，CT 因为其检测小梗塞、小脓肿或(局灶性)脑水肿的灵敏度较低，且脑部 CT 通常不能显示 SAE 患者的特殊表现[5]，MRI 相比 CT 在检测脓毒症患者的脑损害方面更为敏感。脓毒性休克患者发展为急性脑功能障碍时，半数脓毒症患者其头颅 MRI 是异常的[6]。Debora Sanz 在儿童脓毒症的研究中发现最常见的急性脑损伤是缺血和脑炎(即：临床感染背景下的脑水肿/损伤)，这与成人的研究中描述相似[7]，后续多项研究也发现脓毒症患者脑损伤最常见的两种病变是缺血性卒中和白质脑病[6] [8]，弥漫性轴索损伤也有报道[9]。近年来，新的 MRI 序列、MR 波谱、单光子发射计算机断层扫描(SPECT)在阐明 SAE 的病理生理学方面具有很高的潜力。在动物实验中用 T2 加权图像中观察到海马的水表观扩散系数降低[10]，在脓毒症患者的 DWI MRI 中也观察到外侧海马的扩散受限。DWI 信号异常可能提示有谵妄表现的脓毒症患者海马体功能出现改变，它会导致海马体在 DWI MRI 扫描中变得高信号[11]。MR 光谱学用于 SAE 的研究则监测到 N-乙酰天冬氨酸/胆碱(NAA/Cr)比值在脓毒症小鼠中有不同程度的降低[10] [12]。在 SPECT 用于脓毒症的研究中，有研究发现[^{125}I] CLINME 和[^{99m}Tc] HMPAO 可分别用于检测全身炎症早期(注射后 4 小时)的小胶质细胞活化和脑灌注不足[13]。这些对于 SAE 生理病理方面的研究为 SAE 的早期诊断提供了新的前景，但都还需进一步研究。这些研究往往聚焦于脓毒症患

者大脑的急性期病变，Sandquist 等人在儿童 SAE 的研究中重点关注了 SAE 头颅影像的长期异常而非急性期变化[14]，这为我们以后脓毒症患者神经影像学检查的应用提供了一个新的思路。

3. 神经电生理检查

3.1. 脑电图(Electroencephalogram, EEG)

对于脓毒症患者，EEG 比我们通过临床诊断标准诊断脓毒症相关性脑病更敏感，脑电图是脓毒症相关性脑病患者脑功能监测的敏感指标，尤其适用于脓毒症患者的重症监护[15]。EEG 有助于在脓毒症的早期阶段、出现脓毒症脑病临床表现前识别脑功能改变[16]。脓毒症患者常出现非惊厥发作和周期性放电，脑电图癫痫发作(ESZs)和周期性癫痫样放电(PEDs) [17] [18]。SAE 患者会存在明显的全身性 theta 活动，这种 I 级神经元功能障碍主要见于脓毒症相关性脑病，与良好的临床结局相关[19] [20]。Berisavac 等人在一个 39 名 SAE 患者的小队列研究中也发现脓毒症患者存活组中最常见的是 theta 活动，当出现病情恶化时，患者更有可能出现脑电抑制，而不太可能有 theta 活动。TW 波、脑电活动抑制、脑电图反应性缺乏往往与死亡相关[21]。另外三项研究也证实了脑电图反应性缺乏与死亡相关这一观点[17] [22] [23]。

3.2. 诱发电位(Evoked Potentials, EP)

有部分研究表明，诱发电位(体感诱发电位、听觉诱发电位)的改变也预示着脓毒症患者的脑功能改变[24] [25]。S Rinaldi 对 190 名脓毒症患者进行听觉诱发电位(auditory evoked potential)监测，并将 AAI 作为监测指标发现：脓毒症患者的 AAI 会显著降低，脓毒症相关性脑病患者与 AAI 的降低也显著相关，且脓毒症相关性脑病的发展与亚临床脓毒症相关性脑病的发展相比，AAI 的下降幅度更大。因此，AAI 的测定有可能成为确定亚临床脓毒症相关性脑病的可靠诊断试验[24]。体感诱发电位(Somatosensory Evoked Potential, SEP)的短潜伏期和长潜伏期记录也是评估脓毒症代谢性脑病的可靠技术[26]。测量短潜伏期和长潜伏期 SEP 可为严重脓毒症或脓毒症休克危重症患者脓毒症脑病的严重程度提供可靠的预测，严重脓毒症和感染性休克患者的峰值潜伏期会显著延长。Christian Zauner 在研究中发现 84%的患者表现出 N20~N70 峰间潜伏期延长，表明这些患者的皮质 SEP 通路存在弥漫性功能障碍，这表明 SEP 峰值潜伏期提供了一种比其他测量方法(如体格检查)更敏感的电生理技术，SEP 对脓毒症相关性脑病的诊断似乎更可靠[25]。

4. 脑灌注及脑氧和评估

4.1. 经颅多普勒超声(Transcranial Doppler Ultrasonography, TCD)

脑灌注不良可能与脓毒症期间的谵妄有关，TCD 可用于评估脓毒症患者的脑灌注情况，它是一种无创和可行的检查。在脓毒症早期，TCD 可以检测到脑血管收缩，TCD 可作为评估危重脓毒症患者脑血管张力和脑灌注的有效工具[26]。TCD 通过测量局部脑血流速度(CBFV)作为评估脑血流灌注的指标，同时也可通过其二级/三级衍生变量(搏动指数、脑自动调节能力)来反映大脑的血流灌注情况。具有脓毒症相关性脑病患者其 CBFV 更低[27] [28]，搏动指数(PI)、脑自动调节能力(Mxa)是作为脑灌注的常用衍生变量，多项研究表明具有脑功能障碍的脓毒症患者，有搏动指数(PI)的升高和脑自动调节能力的受损[26] [28] [29]。在儿童脓毒症研究中发现 SAE 患者的搏动指数(PI)显著高于非 SAE 患者，PI 可作为脓毒症患者发生 SAE 的预测指标[29]，成人脓毒症研究中证实了这一观点，且 PI 具有良好的敏感性和特异性。PI 值 1.3 代表可用于临床的临界点，PI > 1.3 的临界值可作为脓毒症患者出现脑功能障碍的危险因素用于临床[27]。在另一项大型多中心研究中也报告了脓毒症相关的脑功能障碍和 TCD 检测到的大脑自我调节改变之间的显著相关性，作为反映脑自动调节能力指标的 Mxa，具有脓毒症相关脑功能障碍患者的 Mxa 显著

升高，Mxa 预测脓毒症相关脑功能障碍的最佳临界值为 0.18 (敏感性 79%，特异性 47%) [30]。对脓毒症患者的 TCD 监测，除了单纯评估 CBFV 外，对脓毒症患者进行多方面的监测可以更好的了解疾病，并影响患者的管理。

4.2. 近红外光谱(Near-Infrared Spectroscopy, NIRS)

近红外光谱(NIRS)可以无创性地测量局部脑氧合(rSO_2)作为脑血流灌注的指标，脑灌注不良可能与脓毒症期间的谵妄有关[31]，脑组织低氧饱和度是发生谵妄的独立危险因素[32]。Funk、Pfister、Wood 等人均发现谵妄患者的 rSO_2 低于非谵妄患者[33] [34] [35]。Rosenblatt 等人用 rSO_2 衍生指数脑氧饱和度指数(CO_x)来评估谵妄患者的大脑自动调节能力，rSO_2 绝对值和 MAPOPT 绝对值在轻、中、重度谵妄组间差异无统计学意义。相比之下，中度至重度谵妄患者的 CO_x 值显著高于轻度谵妄患者，这提示大脑自我调节功能失调，谵妄的严重程度增加，强调了 CO_x 值升高与神经系统症状的显著恶化相关[36]。

5. 生物标记物

5.1. 炎症标记物

脓毒症作为一种炎症反应，血浆中多种炎症标记物被证实与脑功能障碍具有相关性。巴西的一项前瞻性研究显示血清炎症标志物 STNFR1、STNFR2、脂联素和 IL-1β 升高与危重患者谵妄的发生有关，但是与脓毒症无相关性[37]。但其他的生物标记物被证实与脓毒症患者的脑功能障碍及其预后相关，IL-6、IL-8、IL-10、C4d 和 C5a 水平可能被用作预测脓毒症相关性脑功能障碍不良事件和死亡的生物标志物[38]。在儿童中，脓毒症患儿血清及脑脊液中的 sICAM-1 比健康儿童高，脓毒症相关性脑病患儿与无神经系统症状(仅脓毒症)患儿相比，sICAM-1 有着显著升高[39]。sVCAM-1 对 SAE 也有较好的预测作用，且严重脓毒症患者入院时的 sVCAM-1 水平比入院时的乳酸浓度和其他黏附分子水平更能预测 SAE [40]。Cristiane Damiani Tomasi 的研究证实了他们的观点，且发现 SAE 患者的脑源性神经营养因子、血小板衍生生长因子(PDGF)-AB/BB 和 RANTES 的水平均有升高[41]。

5.2. 神经组织损伤标记物

神经组织损伤标记物作为神经组织损伤的直接证据，近年来的研究表明，神经组织损伤标记物可以作为预测脓毒症相关性脑病预后的指标。在新生儿中，具有 SAE 的患儿脐带血神经元特异性烯醇化酶(NSE)有升高，可作为预测 SAE 的有效指标，且与 6 个月后神经发育障碍相关[42]。S100β 作为另一个经典的标志物，虽有研究表示 S100β 水平升高与脓毒症期间脑病的严重程度无关[43]，但是多项研究证实了 S100β 用于诊断 SAE 的有效性和敏感性，并且与 SAE 的不良预后密切相关[44] [45] [46] [47] [48]。动态检测血清 S100β 水平是一种更好、更有效监测脓毒症相关性脑损伤的方法[46]，且 S100β 水平比 NSE 和格拉斯哥昏迷量表更能反映严重脑病和脑损伤的类型[44]。SAE 患者的血清 GFAP 水平明显高于非 SAE 患者，其与 SAE 的发病率及其病情严重程度和预后有关[49]。对脑损伤生物标志物的研究表明，血清 tau 蛋白水平升高可能反映脑损伤，血清 tau 蛋白水平是 SAE 发生的独立指标，也是严重脓毒症患者 28 天生存率的预测指标[50]。在其他少见的神经损伤标记物中，脓毒症早期血浆 NT-proCNP 的高峰值浓度可能有助于预测进一步病程中 SAE 的出现[51]。神经丝轻链(NfL)水平是评估神经退行性病变的一个新的标志物，Ehler J 等人的研究发现 SAE 患者血清中的 NfL 水平有着显著升高，且与急性期脑损伤的严重程度密切相关，并与 100 天后的功能损害预后相关，且在后续的 MRI 检查中证实了脑损伤程度与 NfL 升高的相关性。SAE 患者脑脊液中的 NfL 升高，死亡患者高于存活者，且与死亡天数相关，这体现了 NfL 对于 SAE 的预后价值[52]。其他 miRNA、氨基苯乙酸等新的标志物似乎是一些更有前景的生物标记物[53] [54]，

但目前研究较少。

6. 结语

SAE 是脓毒症患者急性期的一种常见并发症，有着较高的发病率及死亡率。目前临床上缺乏特异性的诊断方法，虽然越来越多的研究表明对脓毒症患者进行脑功能监测(神经影像学监测、神经电生理检查、脑氧和及脑灌注监测、生物标志物检测等)对脓毒症患者脑损伤的早期诊断、处理及预测预后有一定的参考价值，但各种监测方式均有各自的优缺点，只有在多模态监测平台下对患者进行多层面、多角度的监测，才能更加全面的评估脓毒症患者的脑损伤情况。且这些研究多是对部分患者的研究，仍缺乏强有力的证据去推荐在临床中广泛应用，未来还需更多大样本的前瞻性研究去进一步验证。

参考文献

[1] Singer, M., Deutschman, C.S., Seymour, C.W., *et al*. (2016) The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). *JAMA*, **315**, 775-787. https://doi.org/10.1001/jama.2016.0287

[2] Gofton, T.E. and Young, G.B. (2012) ENDNOTE Sepsis-Associated Encephalopathy. *Nature Reviews Neurology*, **8**, 557-566. https://doi.org/10.1038/nrneurol.2012.183

[3] Sprung, C.L., Peduzzi, P.N., Shatney, C.H., *et al*. (1990) Impact of Encephalopathy on Mortality in the Sepsis Syndrome. The Veterans Administration Systemic Sepsis Cooperative Study Group. *Critical Care Medicine*, **18**, 801-806. https://doi.org/10.1097/00003246-199008000-00001

[4] Iwashyna, T.J. (2010) Long-Term Cognitive Impairment and Functional Disability among Survivors of Severe Sepsis. *JAMA*: *Journal of the American Medical Association*, **304**, 1787-1794. https://doi.org/10.1001/jama.2010.1553

[5] Cotena, S. and Piazza, O. (2012) Sepsis-Associated Encephalopathy. *Translational Medicine @ UniSa*, **2**, 20-27.

[6] Polito, A., Eischwald, F., Maho, A., *et al*. (2013) Pattern of Brain Injury in the Acute Setting of Human Septic Shock. *Critical Care* (*London*, *England*), **17**, R204. https://doi.org/10.1186/cc12899

[7] Sanz, D., *et al*. (2018) Incidence and Pattern of Brain Lesions in Paediatric Septic Shock Patients. *British Journal of Radiology*, **91**, Article ID: 20170861. https://doi.org/10.1259/bjr.20170861

[8] Abe, S., Okumura, A., Fujii, T., *et al*. (2008) Sepsis Associated Encephalopathy in an Infant with Biliary Atresia. *Brain & Development*, **30**, 544-547. https://doi.org/10.1016/j.braindev.2007.12.015

[9] Ehler, J., Barrett, L.K., Taylor, V., *et al*. (2017) Translational Evidence for Two Distinct Patterns of Neuroaxonal Injury in Sepsis: A Longitudinal, Prospective Translational Study. *Critical Care*, **21**, 262. https://doi.org/10.1186/s13054-017-1850-7

[10] Bozza, F.A., Garteiser, P., Oliveira, M.F., Doblas, S., Cranford, R., *et al*. (2010) Sepsis-Associated Encephalopathy: A Magnetic Resonance Imaging and Spectroscopy Study. *Journal of Cerebral Blood Flow & Metabolism*, **30**, 440-448. https://doi.org/10.1038/jcbfm.2009.215

[11] Zivkovic, A.R., Sedlaczek, O., von Haken, R., *et al*. (2015) Muscarinic M1 Receptors Modulate Endotoxemia-Induced Loss of Synaptic Plasticity. *Acta Neuropathologica Communications*, **3**, 67. https://doi.org/10.1186/s40478-015-0245-8

[12] Wen, M., Lian, Z., Huang, L., *et al*. (2017) Magnetic Resonance Spectroscopy for Assessment of Brain Injury in the Rat Model of Sepsis. *Experimental & Therapeutic Medicine*, **14**, 4118-4124. https://doi.org/10.3892/etm.2017.5034

[13] Szöllősi, D., Hegedűs, N., Veres, D.S., Futó, I. and Horváth, I. (2018) Evaluation of Brain Nuclear Medicine Imaging Tracers in a Murine Model of Sepsis-Associated Encephalopathy. *Molecular Imaging and Biology*, **20**, 952-962. https://doi.org/10.1007/s11307-018-1201-3

[14] Sandquist, M.K., Clee, M.S., Patel, S.K., *et al*. (2017) High Frequency of Neuroimaging Abnormalities among Pediatric Patients with Sepsis Who Undergo Neuroimaging. *Pediatric Critical Care Medicine*, **18**, 607-613. https://doi.org/10.1097/PCC.0000000000001173

[15] Young, G.B., Bolton, C.F., Archibald, Y.M., Austin, T.W. and Wells, G.A. (1992) The Electroencephalogram in Sepsis-Associated Encephalopathy. *Journal of Clinical Neurophysiology*, **9**, 145-152. https://doi.org/10.1097/00004691-199201000-00016

[16] Velissaris, D., Pantzaris, N.D., Skroumpelou, A., *et al*. (2018) Electroencephalographic Abnormalities in Sepsis Patients in Correlation to the Calculated Prognostic Scores: A Case Series. *Journal of Translational Internal Medicine*, **6**, 176-180. https://doi.org/10.2478/jtim-2018-0032

[17] Gilmore, E.J., Gaspard, N., Choi, H.A., *et al*. (2015) Acute Brain Failure in Severe Sepsis: A Prospective Study in the Medical Intensive Care Unit Utilizing Continuous EEG Monitoring. *Intensive Care Medicine*, **41**, 686-694. https://doi.org/10.1007/s00134-015-3709-1

[18] Oddo, M., Carrera, E., Claassen, J., *et al*. (2009) Continuous Electroencephalography in the Medical Intensive Care Unit. *Critical Care Medicine*, **37**, 2051-2056. https://doi.org/10.1097/CCM.0b013e3181a00604

[19] Alkhamis, F. and Nazish, S. (2020) Electroencephalographic Grading of Neuronal Dysfunction in Various Etiologies of Encephalopathy. *Clinical EEG and Neuroscience*, **51**, 420-425. https://doi.org/10.1177/1550059420925962

[20] Nazish, S., Zafar, A., Shariff, E., *et al*. (2021) Clinical Correlates of Electroencephalographic Patterns in Critically Ill Patients. *Clinical EEG and Neuroscience*, **52**, 287-295. https://doi.org/10.1177/1550059420966844

[21] Berisavac, I.I., Padjen, V.V., Ercegovac, M.D., *et al*. (2016) Focal Epileptic Seizures, Electroencephalography and Outcome of Sepsis Associated Encephalopathy—A Pilot Study. *Clinical Neurology and Neurosurgery*, **148**, 60-66. https://doi.org/10.1016/j.clineuro.2016.06.013

[22] Azabou, E., Magalhaes, E., Braconnier, A., *et al*. (2015) Early Standard Electroencephalogram Abnormalities Predict Mortality in Septic Intensive Care Unit Patients. *PLOS ONE*, **10**, e0139969. https://doi.org/10.1371/journal.pone.0139969

[23] Kurtz, P., Gaspard, N., Wahl, A.S., *et al*. (2014) Continuous Electroencephalography in a Surgical Intensive Care Unit. *Intensive Care Medicine*, **40**, 228-234. https://doi.org/10.1007/s00134-013-3149-8

[24] Rinaldi, S., Consales, G. and De Gaudio, A.R. (2008) Changes in Auditory Evoked Potentials Induced by Postsurgical Sepsis. *Minerva Anestesiologica*, **74**, 245-250.

[25] Zauner, C., Gendo, A., Kramer, L., *et al*. (2002) Impaired Subcortical and Cortical Sensory Evoked Potential Pathways in Septic Patients. *Critical Care Medicine*, **30**, 1136-1139. https://doi.org/10.1097/00003246-200205000-00030

[26] Pierrakos, C., Antoine, A., Velissaris, D., *et al*. (2013) Transcranial Doppler Assessment of Cerebral Perfusion in Critically Ill Septic Patients: A Pilot Study. *Annals of Intensive Care*, **3**, 28. https://doi.org/10.1186/2110-5820-3-28

[27] Pierrakos, C., Attou, R., Decorte, L., *et al*. (2014) Transcranial Doppler to Assess Sepsis-Associated Encephalopathy in Critically Ill Patients. *BMC Anesthesiology*, **14**, 45. https://doi.org/10.1186/1471-2253-14-45

[28] Szatmári, S., Végh, T., Csomós, A., *et al*. (2010) Impaired Cerebrovascular Reactivity in Sepsis-Associated Encephalopathy Studied by Acetazolamide Test. *Critical Care*, **14**, R50. https://doi.org/10.1186/cc8939

[29] Algebaly, H., ElSherbini, S., Galal, A., *et al*. (2020) Transcranial Doppler Can Predict Development and Outcome of Sepsis-Associated Encephalopathy in Pediatrics with Severe Sepsis or Septic Shock. *Frontiers in Pediatrics*, **8**, 450. https://doi.org/10.3389/fped.2020.00450

[30] Crippa, I.A., Subirà, C., Vincent, J.L., *et al*. (2018) Impaired Cerebral Autoregulation Is Associated with Brain Dysfunction in Patients with Sepsis. *Critical Care*, **22**, 327. https://doi.org/10.1186/s13054-018-2258-8

[31] Wood, M.D., Boyd, J.G., Wood, N., *et al*. (2022) The Use of Near-Infrared Spectroscopy and/or Transcranial Doppler as Non-Invasive Markers of Cerebral Perfusion in Adult Sepsis Patients with Delirium: A Systematic Review. *Journal of Intensive Care Medicine*, **37**, 408-422. https://doi.org/10.1177/0885066621997090

[32] Wood, M.D., Maslove, D.M., Muscedere, J.G., *et al*. (2017) Low Brain Tissue Oxygenation Contributes to the Development of Delirium in Critically Ill Patients: A Prospective Observational Study. *Journal of Critical Care*, **41**, 289-295. https://doi.org/10.1016/j.jcrc.2017.06.009

[33] Funk, D.J., Kumar, A. and Klar, G. (2016) Decreases in Cerebral Saturation in Patients with Septic Shock Are Associated with Increased Risk of Death: A Prospective Observational Single Center Study. *Journal of Intensive Care*, **4**, 42. https://doi.org/10.1186/s40560-016-0167-y

[34] Pfister, D., Siegemund, M., Dell-Kuster, S., *et al*. (2008) Cerebral Perfusion in Sepsis-Associated Delirium. *Critical Care*, **12**, R63. https://doi.org/10.1186/cc6891

[35] Wood, M., Song, A., Maslove, D., *et al*. (2016) Brain Tissue Oxygenation in Patients with Septic Shock: A Feasibility Study. *Canadian Journal of Neurological Sciences*, **43**, 65-73. https://doi.org/10.1017/cjn.2015.280

[36] Rosenblatt, K., Walker, K.A., Goodson, C., *et al*. (2020) Cerebral Autoregulation-Guided Optimal Blood Pressure in Sepsis-Associated Encephalopathy: A Case Series. *Journal of Intensive Care Medicine*, **35**, 1453-1464. https://doi.org/10.1177/0885066619828293

[37] Ritter, C., Tomasi, C.D., Dal-Pizzol, F., *et al*. (2014) Inflammation Biomarkers and Delirium in Critically Ill Patients. *Critical Care*, **18**, R106. https://doi.org/10.1186/cc13887

[38] Orhun, G., Tüzün, E., Özcan, P.E., *et al*. (2019) Association between Inflammatory Markers and Cognitive Outcome in Patients with Acute Brain Dysfunction Due to Sepsis. *Noro Psikiyatri Arsivi*, **56**, 63-70. https://doi.org/10.29399/npa.23212

[39] Hamed, S.A., Hamed, E.A. and Abdella, M.M. (2009) Septic Encephalopathy: Relationship to Serum and Cerebros-

pinal Fluid Levels of Adhesion Molecules, Lipid Peroxides and S-100B Protein. *Neuropediatrics*, **40**, 66-72. https://doi.org/10.1055/s-0029-1231054

[40] Su, C.M., Cheng, H.H., Tsai, T.C., *et al*. (2014) Elevated Serum Vascular Cell Adhesion Molecule-1 Is Associated with Septic Encephalopathy in Adult Community-Onset Severe Sepsis Patients. *BioMed Research International*, **2014**, Article ID: 598762. https://doi.org/10.1155/2014/598762

[41] Tomasi, C.D., Vuolo, F., Generoso, J., *et al*. (2017) Biomarkers of Delirium in a Low-Risk Community-Acquired Pneumonia-Induced Sepsis. *Molecular Neurobiology*, **54**, 722-726. https://doi.org/10.1007/s12035-016-9708-6

[42] El Shimy, M.S., El-Raggal, N.M., El-Farrash, R.A., *et al*. (2018) Cerebral Blood Flow and Serum Neuron-Specific Enolase in Early-Onset Neonatal Sepsis. *Pediatric Research*, **84**, 261-266. https://doi.org/10.1038/s41390-018-0062-4

[43] Piazza, O., Russo, E., Cotena, S., *et al*. (2007) Elevated S100B Levels Do Not Correlate with the Severity of Encephalopathy during Sepsis. *British Journal of Anaesthesia*, **99**, 518-521. https://doi.org/10.1093/bja/aem201

[44] Nguyen, D.N., Spapen, H., Su, F., *et al*. (2006) Elevated Serum Levels of S-100beta Protein and Neuron-Specific Enolase Are Associated with Brain Injury in Patients with Severe Sepsis and Septic Shock. *Critical Care Medicine*, **34**, 1967-1974. https://doi.org/10.1097/01.CCM.0000217218.51381.49

[45] Spapen, H., Nguyen, D.N., Troubleyn, J., *et al*. (2010) Drotrecogin Alfa (Activated) May Attenuate Severe Sepsis-Associated Encephalopathy in Clinical Septic Shock. *Critical Care*, **14**, R54. https://doi.org/10.1186/cc8947

[46] Wu, L., Feng, Q., Ai, M.L., *et al*. (2020) The Dynamic Change of Serum S100B Levels from Day 1 to Day 3 Is More Associated with Sepsis-Associated Encephalopathy. *Scientific Reports*, **10**, Article No. 7718. https://doi.org/10.1038/s41598-020-64200-3

[47] Yao, B., Zhang, L.N., Ai, Y.H., *et al*. (2014) Serum S100*β* Is a Better Biomarker than Neuron-Specific Enolase for Sepsis-Associated Encephalopathy and Determining Its Prognosis: A Prospective and Observational Study. *Neurochemical Research*, **39**, 1263-1269. https://doi.org/10.1007/s11064-014-1308-0

[48] Zhang, L., Jiang, Y., Deng, S., *et al*. (2021) S100B/RAGE/Ceramide Signaling Pathway Is Involved in Sepsis-Associated Encephalopathy. *Life Sciences*, **277**, 119490. https://doi.org/10.1016/j.lfs.2021.119490

[49] 颜姗珊, 高敏, 陈欢, 等. 脓毒症相关性脑病患者血清胶质纤维酸性蛋白的表达及其临床意义[J]. 中南大学学报: 医学版, 2019, 44(10): 1137-1142.

[50] Zhao, T., Xia, Y., Wang, D. and Pang, L. (2019) Association between Elevated Serum Tau Protein Level and Sepsis-Associated Encephalopathy in Patients with Severe Sepsis. *Canadian Journal of Infectious Diseases and Medical Microbiology*, **2019**, Article ID: 1876174. https://doi.org/10.1155/2019/1876174

[51] Ehler, J., Saller, T., Wittstock, M., *et al*. (2019) Diagnostic Value of NT-proCNP Compared to NSE and S100B in Cerebrospinal Fluid and Plasma of Patients with Sepsis-Associated Encephalopathy. *Neuroscience Letters*, **692**, 167-173. https://doi.org/10.1016/j.neulet.2018.11.014

[52] Ehler, J., Petzold, A., Wittstock, M., *et al*. (2019) The Prognostic Value of Neurofilament Levels in Patients with Sepsis-Associated Encephalopathy—A Prospective, Pilot Observational Study. *PLOS ONE*, **14**, e0211184. https://doi.org/10.1371/journal.pone.0211184

[53] Osca-Verdegal, R., Beltrán-García, J., Pallardó, F.V. and García-Giménez, J.L. (2021) Role of microRNAs as Biomarkers in Sepsis-Associated Encephalopathy. *Molecular Neurobiology*, **58**, 4682-4693. https://doi.org/10.1007/s12035-021-02445-3

[54] Zhu, J., Zhang, M., Han, T., *et al*. (2019) Exploring the Biomarkers of Sepsis-Associated Encephalopathy (SAE): Metabolomics Evidence from Gas Chromatography-Mass Spectrometry. *BioMed Research International*, **2019**, Article ID: 2612849. https://doi.org/10.1155/2019/2612849