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弥漫性轴索损伤患者血清 MBP、IL-1 β 、IL-8 及 TNF- α 水平的表达及临床意义*

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摘要 目的:探讨弥漫性轴索损伤(DAI)患者血清髓鞘碱性蛋白(MBP)、白细胞介素-1 β (IL-1 β)、白细胞介素-8(IL-8)及肿瘤坏死因子- α (TNF- α)水平的表达及临床意义。**方法:**选取2015年12月-2018年1月我院神经外科收治的DAI患者90例作为观察组,另选取在我院体检的健康志愿者30例作为对照组,并根据格拉斯哥昏迷评分(GCS)将观察组患者分为重度组(42例)、中度组(30例)、轻度组(18例)。对比观察组和对照组血清MBP、IL-1 β 、IL-8及TNF- α 水平,比较观察组患者不同严重程度、伤后不同时间血清MBP、IL-1 β 、IL-8及TNF- α 水平。**结果:**观察组患者血清中的MBP、IL-1 β 、IL-8及TNF- α 水平显著高于对照组($P<0.05$)。重度组患者血清MBP、IL-1 β 、IL-8及TNF- α 水平显著高于中度组和轻度组,且中度组显著高于轻度组($P<0.05$)。伤后不同时间观察组患者血清MBP、IL-1 β 、IL-8及TNF- α 水平整体比较差异均有统计学意义($P<0.05$);其中MBP水平在伤后前期到伤后3d持续升高($P<0.05$);IL-1 β 、IL-8、TNF- α 水平在伤后前期到伤后2d持续升高,在伤后3d呈下降趋势($P<0.05$)。**结论:**DAI患者血清MBP、IL-1 β 、IL-8及TNF- α 水平偏高,临床通过检测这四种血清指标水平,有助于评估患者的病情。

关键词:弥漫性轴索损伤;髓鞘碱性蛋白;白细胞介素-1 β ;白细胞介素-8;肿瘤坏死因子- α

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Expression and Clinical Significance of Serum MBP, IL-1 β , IL-8 and TNF- α Levels in Patients with Diffuse Axonal Injury*

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ABSTRACT Objective: To investigate the expression of serum myelin basic protein (MBP), interleukin-1 β (IL-1 β), interleukin-8 (IL-8) and tumor necrosis factor- α (TNF- α) in patients with diffuse axonal injury (DAI) and its clinical significance. **Methods:** A total of 90 patients with DAI, who were admitted to Department of neurosurgery in Xi'an Gaoxin Hospital from December 2015 to January 2018, were selected as observation group; another 30 healthy volunteers, whose physical examination results were normal, as control group. The patients in the observation group were again divided into severe group ($n=42$), moderate group ($n=30$) and mild group ($n=18$) according to the Glasgow coma scale (GCS). The levels of serum MBP, IL-1 β , IL-8 and TNF- α were compared between the observation group and the control group. The levels of serum MBP, IL-1 β , IL-8 and TNF- α of patients in the observation group with different severity and time were compared. **Results:** The levels of serum MBP, IL-1 β , IL-8 and TNF- α in the observation group were significantly higher than those in the control group ($P<0.05$). The levels of serum MBP, IL-1 β , IL-8 and TNF- α in the severe group were significantly higher than those in the moderate group and the mild group, and the moderate group was significantly higher than the mild group ($P<0.05$). The levels of serum MBP, IL-1 β , IL-8 and TNF- α in the observation group were statistically significant at different time after injury ($P<0.05$), in which, the level of MBP remained elevated from the early stage after injury to 3d after injury ($P<0.05$); the levels of IL-1 β , IL-8, TNF- α remained elevated from the early stage after injury to 2d after injury, decreasing 3d after injury ($P<0.05$). **Conclusion:** The levels of serum MBP, IL-1 β , IL-8 and TNF- α are higher in DAI patients. The clinical detection of these four serum markers can help doctors assess the conditions of the patients.

Key words: Diffuse axonal injury; Myelin basic protein; Interleukin-1 β ; Interleukin-8; Tumor necrosis factor- α

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前言

弥漫性轴索损伤(Diffuse axonal injury, DAI)是指头部在受到强烈的外部作用力后,脑内出现以神经轴索断裂为主要病理特征的脑实质性损伤^[1,2]。DAI患者往往长时间昏迷,且容易并发其他类型的脑损伤,患者在清醒后多伴有意识障碍,临床治疗难度大,患者致死率、致残率较高^[3-5]。目前临床上常用检测疾病相关血清学指标的方法来分析患者病情,DAI患者通常伴有中枢神经系统受损和炎症反应,检测相关的血清学指标可以判断患者病情、评估预后^[6,7]。髓鞘碱性蛋白(myelin basic protein, MBP)是一种含有多种碱性氨基酸的强碱性膜蛋白,其水平可评估中枢神经系统的状态^[8,9]。白细胞介素-1 β (interleukin 1 β , IL-1 β)和白细胞介素-8(interleukin 8, IL-8)均是白细胞介素家族的成员,是一种可以反映体内炎症反应程度的因子^[10]。肿瘤坏死因子- α (tumor necrosis factor α , TNF- α)是一种由巨噬细胞和T细胞分泌的因子,具有调节免疫、介导炎症反应、抗肿瘤等作用^[11]。本研究旨在探讨DAI患者血清MBP、IL-1 β 、IL-8及TNF- α 水平的表达及临床意义,以进一步了解四种血清学指标与DAI的关系,现将研究结果整理如下。

1 资料与方法

1.1 一般资料

选取2015年12月-2018年1月我院神经外科收治的DAI患者90例作为观察组,纳入标准^[12]:①所有患者均经CT影像确诊为DAI,即在大脑髓质与皮质的交界处、基底节内囊等区域有明显的点状高密度影;②有明确的致伤原因,且在脑部有明显的因加速度而受到的损伤;③患者家属对本次研究知情同意。排除标准:①患有其他脑部疾病者;②合并有其他严重器质性疾病者;③大量硬膜下积液者。观察组男51例,女39例,年龄27-61岁,平均(37.83 $\pm$ 8.71)岁,致伤原因:交通意外

53例,高处坠落22例,击打8例,其他7例。另选取在我院体检的健康志愿者30例作为对照组,其中男18例,女12例,年龄25-63岁,平均(38.16 $\pm$ 8.92)岁。两组受试者的年龄、性别比较差异无统计学意义($P>0.05$),具有可比性。另根据格拉斯哥昏迷评分^[13](Glasgow coma score, GCS)将观察组患者分为重度组($n=42$)、中度组($n=30$)、轻度组($n=18$),分组标准:GCS ≤ 8 分为重度,9分 $\leq$ GCS ≤ 12 分为中度, GCS ≥ 13 分为轻度。研究经我院伦理委员会审核通过。

1.2 方法

抽取观察组患者伤后前期(小于6h)、伤后1d、伤后2d、伤后3d的静脉血5 mL,对照组于体检时抽取清晨空腹静脉血5 mL,将所有研究对象的血液进行离心处理,以3000 r/min的转速离心10 min,取其上层血清进行相关检测。采用酶联免疫吸附法检测所有研究对象血清中MBP、IL-1 β 、IL-8及TNF- α 水平,其中MBP试剂盒购于北京乐博生物科技有限公司,IL-1 β 、IL-8试剂盒购于上海恒远生物科技有限公司, TNF- α 试剂盒购于南京森贝伽生物科技有限公司,所有检验工作由我院两名专业的检验人员完成,具体步骤均严格遵循试剂盒说明书中的操作指南。

1.3 统计学方法

所有数据均用SPSS19.0进行统计分析,计数资料以率(%)的形式表示,采用卡方检验,计量资料以($\bar{x}\pm s$)的形式表示,采用t检验,多组间计量资料比较采用F检验,以 $P<0.05$ 为差异有统计学意义。

2 结果

2.1 观察组和对照组血清MBP及炎症因子水平比较

观察组患者血清中的MBP、IL-1 β 、IL-8及TNF- α 水平显著高于对照组($P<0.05$),具体见表1。

表1 观察组和对照组血清MBP、IL-1 β 、IL-8及TNF- α 水平比较($\bar{x}\pm s$)

Table 1 Comparison of serum MBP, IL-1 β , IL-8, TNF- α levels between observation group and control group($\bar{x}\pm s$)

Groups	n	MBP(ng/mL)	IL-1 β (pg/mL)	IL-8(μ g/L)	TNF- α (μ g/L)
Observation group	90	95.43 $\pm$ 36.58	64.87 $\pm$ 10.98	0.33 $\pm$ 0.05	1.30 $\pm$ 0.21
Control group	30	39.67 $\pm$ 4.12	10.64 $\pm$ 2.13	0.09 $\pm$ 0.02	0.82 $\pm$ 0.13
t	-	8.308	26.812	25.559	11.771
P	-	0.000	0.000	0.000	0.000

2.2 观察组不同严重程度的患者血清MBP及炎症因子水平比较

观察组不同严重程度的患者血清MBP、IL-1 β 、IL-8及TNF- α 水平整体比较差异有统计学意义($P<0.05$),重度组患者血清MBP、IL-1 β 、IL-8及TNF- α 水平显著高于中度组和轻度组,且中度组显著高于轻度组($P<0.05$),具体见表2。

2.3 伤后不同时间观察组血清MBP及炎症因子水平比较

伤后不同时间观察组患者血清MBP、IL-1 β 、IL-8及TNF- α 水平整体比较均有统计学意义($P<0.05$);其中MBP水平在伤后前期到伤后3d持续升高($P<0.05$);IL-1 β 、IL-8、

TNF- α 水平在伤后前期到伤后2d持续升高,在伤后3d呈下降趋势($P<0.05$)。具体见表3。

3 讨论

DAI患者由于受到剧烈的外伤,导致颅脑产生角加速度,致使脑组织内部出现剪力作用,神经轴索和小血管因受力过度造成损伤,因此DAI可以看作是一种头部加速度运动导致的脑深部应变性受损^[14,15]。DAI患者的损伤多发于白质和灰质交界处、小脑与大脑间的脑干头端、脑半球之间的胼胝体等不同组织结构之间^[16,17]。交通意外是造成DAI的主要原因,随着交

表 2 观察组不同严重程度的患者血清 MBP、IL-1 β 、IL-8 及 TNF- α 水平比较($\bar{x}\pm s$)Table 2 Comparison of serum MBP, IL-1 β , IL-8, TNF- α levels of patients with different severity in observation group($\bar{x}\pm s$)

Groups	n	MBP(ng/mL)	IL-1 β (pg/mL)	IL-8(μ g/L)	TNF- α (μ g/L)
Mild group	18	71.56 $\pm$ 31.09	37.54 $\pm$ 11.36	0.22 $\pm$ 0.05	1.08 $\pm$ 0.17
Moderate group	30	96.23 $\pm$ 27.83 ^a	65.07 $\pm$ 10.42 ^a	0.31 $\pm$ 0.04 ^a	1.30 $\pm$ 0.21 ^a
Severe group	42	112.17 $\pm$ 41.38 ^{ab}	88.67 $\pm$ 12.45 ^{ab}	0.42 $\pm$ 0.06 ^{ab}	1.53 $\pm$ 0.18 ^{ab}
F	-	18.362	24.715	21.392	14.058
P	-	0.000	0.000	0.000	0.000

Note: Compared with mild group, ^a $P<0.05$; Compared with moderate group, ^b $P<0.05$.

表 3 伤后不同时间观察组血清 MBP、IL-1 β 、IL-8 及 TNF- α 水平比较($\bar{x}\pm s$)Table 3 Comparison of serum MBP, IL-1 β , IL-8, TNF- α levels at different time after injury of observation group($\bar{x}\pm s$)

Groups	n	MBP(ng/mL)	IL-1 β (pg/mL)	IL-8(μ g/L)	TNF- α (μ g/L)
Early post injury	90	95.43 $\pm$ 36.58	64.87 $\pm$ 10.98	0.33 $\pm$ 0.05	1.30 $\pm$ 0.21
1d after injury	90	99.65 $\pm$ 34.27 ^a	101.14 $\pm$ 11.24 ^a	0.62 $\pm$ 0.06 ^a	1.54 $\pm$ 0.27 ^a
2d after injury	90	106.73 $\pm$ 42.74 ^{ab}	106.63 $\pm$ 10.37 ^{ab}	0.79 $\pm$ 0.04 ^{ab}	1.82 $\pm$ 0.18 ^{ab}
3d after injury	90	113.06 $\pm$ 40.31 ^{abc}	88.09 $\pm$ 11.54 ^c	0.71 $\pm$ 0.05 ^c	1.63 $\pm$ 0.19 ^c
F	-	26.974	35.268	24.951	19.363
P	-	0.000	0.000	0.000	0.000

Note: Compared with early post injury, ^a $P<0.05$; Compared with 1d after injury, ^b $P<0.05$; Compared with 2d after injury, ^c $P<0.05$.

通意外案例的逐年增加,DAI 患者的数量也逐年递增,给患者及其家庭造成了巨大的伤害,因此探究和 DAI 相关的指标来诊断疾病、了解病情、评估预后具有重要的意义^[18-20]。本研究对比了健康人群和 DAI 患者、不同严重程度的 DAI 患者以及 DAI 患者在伤后不同时间的 MBP、IL-1 β 、IL-8 及 TNF- α 水平,旨在初步探讨四种指标和 DAI 的联系。

在本次研究中,观察组患者血清中 MBP 水平显著高于对照组,重度组患者血清 MBP 水平显著高于中度组和轻度组,中度组患者血清 MBP 水平显著高于轻度组,且 MBP 水平在伤后前期到伤后 3d 持续升高。这说明在 DAI 患者血清中 MBP 水平升高,且病情越严重 MBP 水平越高,随着时间的推移,MBP 水平会跟随着患者病情的改变而改变,上述结果可以说明 MBP 和 DAI 存在一定的联系。究其原因,DAI 由于头部受到外力强烈冲击,导致头部受到旋转力,而白质和灰质存在重量差异,因此可以产生剪切力,对血脑屏障和轴突髓鞘结构造成损伤,此时大量 MBP 流入脑脊液,同时由于血脑屏障受损,因此 MBP 可以流入血液中,造成血清中 MBP 水平升高^[21]。病情较轻的 DAI 患者,血脑屏障和轴突髓鞘结构受损较为轻微,可以适当限制 MBP 进入血液,因此 MBP 水平和 DAI 患者的病情严重程度相关^[22]。DAI 患者在受伤后脑组织发生水肿,出现缺血、缺氧性坏死,导致白质髓鞘受损更加严重,同时血脑屏障通透性增高,进一步导致血清中 MBP 水平升高^[23-25]。由此可见 MBP 水平和 DAI 具有一定的内在联系,检测 MBP 水平可以评估 DAI 患者病情。本次研究结果显示,观察组患者血清中的 IL-1 β 、IL-8 及 TNF- α 水平显著高于对照组,重度组患者血清 IL-1 β 、IL-8 及 TNF- α 水平显著高于中度组和轻度组,中度组患者血清 IL-1 β 、IL-8 及 TNF- α 水平显著高于轻度组,同时 IL-1 β 、IL-8、TNF- α 水平在伤后前期到伤后 2d 持续升高,在伤后 3d

开始下降。这说明在 DAI 患者血清中 IL-1 β 、IL-8 及 TNF- α 水平升高,且 IL-1 β 、IL-8 及 TNF- α 水平随着 DAI 患者病情严重程度的改变而改变。究其原因,DAI 患者脑部组织受到剪力损伤后会出现局部的炎症反应,当中枢神经系统受损后,其外周器官的免疫功能被激活,释放免疫调节物质,同时小胶质细胞被激活,进行分裂增殖,适量的小胶质细胞能对受损细胞起到修复的作用,但是增殖过度会促进其他活性因子的分泌,如 IL-1 β 、IL-8、TNF- α 、干扰素、集落刺激因子等,导致 DAI 患者血清中 IL-1 β 、IL-8 及 TNF- α 水平升高^[26-28]。IL-1 β 、IL-8、TNF- α 等炎性因子可进一步促进炎症反应,导致炎症加剧,使患者病情加重,形成恶性循环^[29,30],因此 IL-1 β 、IL-8、TNF- α 水平和 DAI 患者病情严重程度有关,并且随着时间的推移其水平会随着患者的病情变化而变化。

综上所述,DAI 患者血清中 MBP、IL-1 β 、IL-8 及 TNF- α 水平明显升高,且与病情严重程度有关,随着时间的推移其水平会随着患者的病情变化而变化,临床上检测上述四种指标可评估患者的疾病情况。

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