

doi: 10.13241/j.cnki.pmb.2021.22.021

脊柱骨折合并脊髓损伤患者血清 Neuritin、NFL、S100B 蛋白水平与术后预后不良的关系研究 *

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摘要 目的:研究脊柱骨折合并脊髓损伤(SCI)患者血清神经突起因子(Neuritin)、神经丝轻链(NFL)、S100B 蛋白水平与术后预后不良的关系。**方法:**将从 2018 年 12 月-2019 年 12 月我院收治的 60 例脊柱骨折合并 SCI 患者纳入研究,记作损伤组,另取同期我院收治的单纯脊柱骨折未合并 SCI 患者 60 例作为无损伤组,再取同期体检的健康志愿者 60 例作为对照组。检测并比较三组血清 Neuritin、NFL、S100B 蛋白水平。此外,将损伤组患者按照术后预后的不同分作预后不良组 25 例和预后良好组 35 例,分析两组血清 Neuritin、NFL、S100B 蛋白水平以及临床资料的差异,并以多因素 Logistic 回归分析明确脊柱骨折合并 SCI 患者预后不良和各项影响因素的关系。通过受试者工作特征(ROC)曲线明确血清 Neuritin、NFL、S100B 蛋白水平联合检测预测脊柱骨折合并 SCI 患者预后不良的效能。**结果:**损伤组及无损伤组血清 Neuritin、NFL、S100B 蛋白水平均明显高于对照组,且损伤组上述三项血清学指标水平均高于无损伤组(均 $P<0.05$)。预后不良组椎管侵占率高于预后良好组,且血清 Neuritin、NFL、S100B 蛋白水平均高于预后良好组(均 $P<0.05$)。经多因素 Logistic 回归分析可得:椎管侵占率以及血清 Neuritin、NFL、S100B 蛋白水平较高均是脊柱骨折合并 SCI 患者预后不良的危险因素($P<0.05$)。血清 Neuritin、NFL、S100B 蛋白水平联合检测预测脊柱骨折合并 SCI 患者预后不良的曲线下面积、灵敏度、特异度、约登指数均高于上述三项指标单独检测。**结论:**脊柱骨折合并 SCI 患者血清 Neuritin、NFL、S100B 蛋白水平较高,且随着上述三项血清学指标水平的升高,患者术后不良风险更高。

关键词:脊柱骨折;脊髓损伤;神经突起因子;神经丝轻链;S100B 蛋白;预后

中图分类号:R651.2;R683.2 **文献标识码:**A **文章编号:**1673-6273(2021)22-4303-05

Study the Relationship between Serum Neuritin, NFL, S100B Protein Levels and Poor Postoperative Prognosis in Patients with Spinal Fracture Complicated with Spinal Cord Injury*

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ABSTRACT Objective: To study the relationship between serum neurogenic factor (Neuritin), neural filament light chain (NFL), S100B protein levels and poor postoperative prognosis in patients with spinal fracture complicated with spinal cord injury (SCI). **Methods:** From December 2018 - December 2019, 60 patients with spinal fracture complicated with SCI who were treated in our hospital were included in this study, and classified as injury group. Another 60 cases of patients with simple spinal fracture without SCI admitted in the same period were selected as the non-injury group, and another 60 cases of healthy volunteers receiving physical examination during the same period were selected as the control group. Serum Neuritin, NFL and S100B protein levels were detected and compared in the three groups. In addition, the injury group was divided into poor prognosis group with 25 cases and good prognosis group with 35 cases according to different postoperative prognosis. Serum Neuritin, NFL, S100B protein levels and clinical data differences between the two groups were analyzed, and multivariate Logistic regression analysis was performed to determine the relationship between the poor prognosis and various influencing factors in patients with spinal fracture complicated with SCI. Receiver operating characteristic (ROC) curves were used to determine the efficacy of the combination of serum Neuritin, NFL and S100B protein levels in predicting poor prognosis in patients with spinal fracture complicated with SCI. **Results:** Serum Neuritin, NFL and S100B protein levels in injury group and non-injury group were significantly higher than those in control group, and the above three serological indexes levels in injury group were higher than those in non-injury group (all $P<0.05$). The spinal tract invasion rate in poor prognosis group was higher than that in good prognosis group, and the serum Neuritin, NFL and S100B protein levels were higher than those in good prognosis group (all $P<0.05$).

* 基金项目:广东省中医药局科研项目(20191276)

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(收稿日期:2021-04-07 接受日期:2021-04-30)

Multivariate Logistic regression analysis showed that spinal tract invasion rate and high Neuroitin, NFL and S100B protein levels were the risk factors of poor prognosis in patients with spinal fracture complicated with SCI ($P < 0.05$). The area under the curve, sensitivity, specificity and Youden index of combined detection of serum Neuritin, NFL and S100B protein levels in predicting poor prognosis in patients with spinal fracture complicated with SCI were higher than those of the above three indexes alone. **Conclusions:** Serum Neuritin, NFL, S100B protein levels were higher in patients with spinal fracture complicated with SCI, and the risk of poor prognosis is higher with the increase of the above three serological indexes levels.

Key words: Spinal fracture; Spinal cord injury; Neurogenic factor; Neural filament light chain; S100B protein; Prognosis

Chinese Library Classification(CLC): R651.2; R683.2 **Document code:** A

Article ID: 1673-6273(2021)22-4303-05

前言

脊柱骨折属于骨科临床较为常见的一种疾病,主要是因高处坠落或交通事故等间接外力引起,且约有 1/5 的患者伴有脊髓损伤(SCI)^[1-3]。SCI 的发生会促使患者表现出不同程度的感觉、运动以及自主神经功能异常,且会表现出大小便失禁等多种并发症,对患者的身心健康造成极大的影响^[4-6]。故此,如何有效对患者病情实施评估显得尤为重要。神经突起因子(Neuritin)则是一种新型神经营养因子,在神经系统发育以及神经损伤修复过程中起着至关重要的作用^[7,8]。神经丝轻链(NFL)属于神经元特异性结构蛋白之一,在神经元受损之后会大量释放入血,其活性变化和神经变性疾病息息相关^[9,10]。S100B 蛋白则和神经功能损伤密切相关,且被证实存在脑损伤伴神经功能障碍患者血循环中存在异常高表达^[11]。鉴于此,本文通过研究脊柱骨折合并 SCI 患者血清 Neuritin、NFL、S100B 蛋白水平与术后预后不良的关系,以期对脊柱骨折合并 SCI 患者术后预后评估提供辅助生物学标志物,现作以下报道。

1 对象与方法

1.1 一般资料

将从 2018 年 12 月~2019 年 12 月我院收治的 60 例脊柱骨折合并 SCI 患者纳入研究,记作损伤组。其中男性 36 例,女性 24 例;年龄 21~58 岁,平均(36.34±6.23)岁;受伤原因:高处坠落伤 37 例,交通事故伤 14 例,其它 9 例;发病至手术时长 1.8~10.4 h,平均(6.63±1.59)h;骨折累及节段:T11~T12 有 32 例,L1~L2 有 28 例;术后并发症 8 例;ASIA 分级^[12]:A 级 10 例,B 级 20 例,C 级 24 例,D 级 6 例。另取同期我院收治的单纯脊柱骨折未合并 SCI 患者 60 例作为无损伤组。其中男性 37 例,女性 23 例;年龄 20~59 岁,平均(37.01±6.28)岁;受伤原因:高处坠落伤 40 例,交通事故伤 13 例,其它 7 例;骨折累及节段:T11~T12 有 34 例,L1~L2 有 26 例。再取同期体检的健康志愿者 60 例作为对照组。其中男性 38 例,女性 22 例;年龄 21~58 岁,平均(36.46±6.32)岁。三组性别、年龄比较无统计学差异($P > 0.05$),基线资料均衡,可比性佳。入选标准:(1)所有患者均符合《骨与关节创伤》^[13]中所制定的相关诊断标准,且经 CT 以及 MRI 等影像学检查确诊为脊柱骨折;(2)均于伤后 12h 内入院接受治疗;(3)损伤组与《外科学》^[14]中所制定的 SCI 相关诊断相符;(4)无临床病历资料缺失。剔除标准:(1)合并凝血功能异常或(和)恶性肿瘤者;(2)心、肝、肺等重要脏器发生严重病变者;(3)既往有颅脑损伤史或(和)神经系统疾病

者;(4)妊娠期或哺乳期女性。入组人员均于同意书上签字,我院医学伦理委员会已批准。

1.2 研究方法

(1)临床资料采集:对所有受试者临床资料进行采集、记录,主要包括下述几项:①年龄;②性别;③椎管侵占率;④发病至手术时长;⑤受伤原因;⑥骨折累及节段。(2)血清 Neuritin、NFL、S100B 蛋白水平检测:分别采集所有患者入院后 24 h 时、健康志愿者体检当日的空腹静脉血 5 mL,以 8 cm 为离心半径离心 10 min,获取血清置于冰箱中保存备用,采用酶联免疫吸附法检测血清 Neuritin、NFL、S100B 蛋白水平。操作遵循试剂盒说明书完成,试剂盒均由上海科顺生物科技有限公司提供。(3)分组方式:将损伤组患者按照术后预后的不同分作预后不良组 25 例和预后良好组 35 例。参照 ASIA 分级^[14]对所有受试者进行评估,并将分级相较术前有所改善记作预后良好。

1.3 统计学处理

将 SPSS 22.0 软件作为数据处理工具,计量资料用($\bar{x} \pm s$)表示,采用 t 检验,多组间比较采用重复测量方差分析。计数资料用[n(%)]表示,采用 χ^2 检验。以多因素 Logistic 回归分析明确脊柱骨折合并 SCI 患者预后不良和各项影响因素的关系。通过受试者工作特征(ROC)曲线明确血清 Neuritin、NFL、S100B 蛋白水平联合检测预测脊柱骨折合并 SCI 患者预后不良的效能。 $P < 0.05$ 则表示差异有统计学意义。

2 结果

2.1 三组血清 Neuritin、NFL、S100B 蛋白水平评价

损伤组及无损伤组血清 Neuritin、NFL、S100B 蛋白水平均明显高于对照组,且损伤组上述三项血清学指标水平均高于无损伤组(均 $P < 0.05$)。见表 1。

2.2 不同预后损伤组患者血清 Neuritin、NFL、S100B 蛋白水平以及临床资料评价

预后不良组椎管侵占率高于预后良好组,且血清 Neuritin、NFL、S100B 蛋白水平均高于预后良好组(均 $P < 0.05$);而两组年龄、发病至手术时长、性别、受伤原因、骨折累及节段、术后并发症对比均无统计学差异(均 $P > 0.05$)。见表 2。

2.3 脊柱骨折合并 SCI 患者预后不良影响因素分析

以脊柱骨折合并 SCI 患者预后不良与否为因变量,赋值如下:预后不良=1,预后良好=0。以椎管侵占率以及血清 Neuritin、NFL、S100B 蛋白水平为自变量,赋值如下:椎管侵占率以及血清 Neuritin、NFL、S100B 蛋白水平均为原值输入。经多因素 Logistic 回归分析可得:椎管侵占率以及血清 Neuritin、NFL、

S100B 蛋白水平较高均是脊柱骨折合并 SCI 患者预后不良的危险因素(均 $OR > 1, P < 0.05$)。见表 3。

表 1 三组血清 Neuritin、NFL、S100B 蛋白水平评价($\bar{x} \pm s$)
Table 1 Evaluation of serum Neuroitin, NFL and S100B protein levels in three groups($\bar{x} \pm s$)

Groups	n	Neuritin(ng/L)	NFL(pg/mL)	S100B(μ g/L)
Injury group	60	108.47 $\pm$ 10.54 ^{#*}	67.87 $\pm$ 11.59 ^{#*}	0.62 $\pm$ 0.11 ^{#*}
Non-injury group	60	80.45 $\pm$ 7.13 [#]	29.57 $\pm$ 9.10 [#]	0.39 $\pm$ 0.06 [#]
Control group	60	34.58 $\pm$ 4.10	5.94 $\pm$ 2.05	0.31 $\pm$ 0.02
F	-	15.293	20.745	9.105
P	-	0.000	0.000	0.000

Note: compared with the control group, [#] $P < 0.05$; compared with the non-injury group, ^{*} $P < 0.05$.

表 2 不同预后损伤组患者血清 Neuritin、NFL、S100B 蛋白水平以及临床资料评价
Table 2 Serum Neuritin, NFL, S100B protein levels and clinical data evaluation of different prognosis injury groups

Influence factors	Poor prognosis group (n=25)	Good prognosis group (n=35)	χ^2/t	P
Age(years)	36.23 $\pm$ 6.19	36.41 $\pm$ 6.25	-0.110	0.913
Time from onset to operation(h)	6.61 $\pm$ 1.58	6.64 $\pm$ 1.60	-0.072	0.943
Spinal tract invasion rate(%)	63.21 $\pm$ 10.44	42.06 $\pm$ 6.28	9.779	0.000
Gender	Male	21(60.00)	0.000	1.000
	Female	10(40.00)		
Cause of injury	Fall from height	22(62.85)	0.062	0.805
	Traffic accident	6(24.00)		
	Other	4(16.00)		
Fracture involved segment	T11~T12	19(54.29)	0.031	0.861
	L1~L2	12(48.00)		
Postoperative complications	Yes	5(14.29)	0.066	0.797
	No	30(85.71)		
Neuritin(ng/L)	113.15 $\pm$ 10.60	105.12 $\pm$ 9.48	3.079	0.003
NFL(pg/mL)	77.16 $\pm$ 12.05	61.24 $\pm$ 10.34	5.487	0.000
S100B(μ g/L)	0.72 $\pm$ 0.12	0.55 $\pm$ 0.09	6.274	0.000

表 3 脊柱骨折合并 SCI 患者预后不良影响因素分析
Table 3 Analysis of influencing factors of adverse factors of prognosis in patients with spinal fracture and SCI

Risk factors	Regression coefficient	Standard error	Wald χ^2	P	OR	95%CI
Spinal tract invasion rate	3.195	2.196	9.184	0.012	1.286	1.055~2.327
Serum Neuritin	4.102	3.864	10.394	0.001	2.056	1.412~4.005
Serum NFL	2.977	3.105	10.056	0.002	1.479	1.086~2.115
Serum S100B	3.042	2.386	14.259	0.000	2.152	1.523~4.113
Constant term	-5.286	2.152	-	0.002	0.001	-

2.4 血清 Neuritin、NFL、S100B 蛋白水平诊断脊柱骨折合并 SCI 患者预后不良效能的 ROC 曲线分析

血清 Neuritin、NFL、S100B 蛋白水平联合检测预测脊柱骨折合并 SCI 患者预后不良的曲线下面积、灵敏度、特异度、约登指数均高于上述三项指标单独检测。见表 4。

3 讨论

SCI 属于临床上较为常见的中枢神经系统疾病之一,存在发病率高、致残率高、病死率高的特点,会引起损伤节段以下发生感觉障碍以及多系统功能异常等,从而严重威胁患者的身心

表 4 血清 Neuritin、NFL、S100B 蛋白水平诊断脊柱骨折合并 SCI 患者预后不良效能的 ROC 曲线分析

Table 4 ROC curve analysis of the adverse prognosis of patients with spinal fracture complicated with SCI diagnosed by serum neuritin, NFL and S100B protein levels

Detection indexes	Area under the curve	Threshold value	Sensitivity(%)	Specificity(%)	Youden index
Serum Neuritin	0.691	110.69 ng/L	72.34	68.15	0.405
Serum NFL	0.687	68.31 pg/mL	73.09	64.33	0.374
Serum S100B	0.703	0.64 μ g/L	73.14	67.42	0.406
Three joint projects	0.905	-	91.08	89.48	0.806

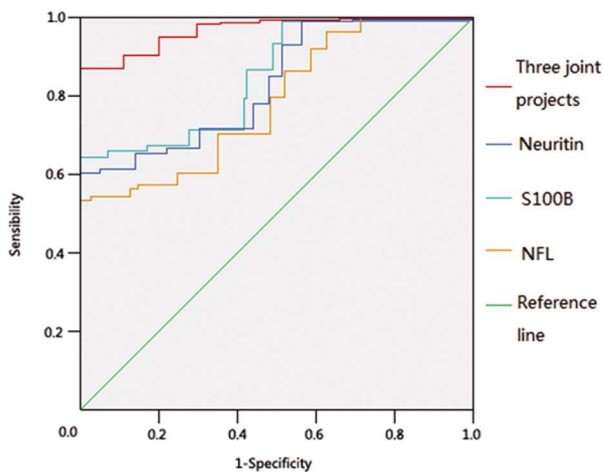


图 1 血清 Neuritin、NFL、S100B 蛋白水平诊断脊柱骨折合并 SCI 患者预后不良效能的 ROC 曲线

Fig. 1 ROC curve of serum Neuritin, NFL and S100B protein levels in the diagnosis of poor prognosis in patients with spinal fracture combined with SCI

健康,并对患者家庭以及社会造成极大的经济负担^[15-17]。迄今为止,临床上针对 SCI 的诊断主要是依靠查体以及影像学检查完成,然而常规检查以及影像学技术均存在一定的局限性,欠缺对 SCI 病情严重程度以及预后评估的客观判断,仍需相关特异性的生化指标实现对脊柱骨折合并 SCI 的辅助诊断^[18-20]。随着近年来相关研究报道的不断深入,越来越多的学者发现血清学生化指标检测因具有无创伤性、可重复性高等特点,开始被广泛应用于临床多种疾病的诊断以及预后评估中,且具有一定的应用价值^[21]。

本研究结果发现,脊柱骨折合并 SCI 患者血清 Neuritin、NFL、S100B 蛋白水平均异常升高。分析原因,Neuritin 主要参与了神经元分化以及血管新生等过程,其广泛表达于血旺细胞内,而血旺细胞属于外周神经髓鞘的重要营养来源,在机体出现 SCI 时,神经脱髓鞘以及神经纤维轴突变性改变,继而引起血旺细胞迁移,促进 Neuritin 通过血脑屏障并进入血液循环中^[22,23]。NFL 广泛表达于轴突白质内,于轴突生长以及细胞内运输过程发挥着至关重要的作用,在患者 SCI 之后会立即引起神经细胞死亡以及组织损伤,之后引起炎症反应以及氧化应激等多种生物化学改变,进一步导致 NFL 水平升高^[24-26]。脊柱骨折患者一旦并发 SCI 会导致血脑屏障遭受破坏,继而促使 S100B 被大量释放进入外周血液循环之内,并在数小时之内升至峰值^[27-29]。此外,经多因素 Logistic 回归分析可得:椎管侵占率以及血清 Neuritin、NFL、S100B 蛋白水平较高均是脊柱骨折合并

SCI 患者预后不良的危险因素,考虑原因,随着置管侵占率的不断增加,患者脊髓压迫程度不断加剧,导致临床治疗难度增加,影响预后。另外,血清 Neuritin、NFL、S100B 蛋白水平主要受血脑屏障破坏以及神经细胞损伤的影响,三者神经细胞受损之后分泌量会出现敏感性升高,且在神经细胞存在持续凋亡或水肿状态下,三者血清浓度会呈现出持续的高值。由此可知,三项血清指标表达水平越高,可在一定程度反映患者的病情较重,临床治疗难度较大,预后不良。本研究结果还显示了血清 Neuritin、NFL、S100B 蛋白水平联合检测预测脊柱骨折合并 SCI 患者预后不良的效能较佳,原因可能和三项指标联合检测具有一定的协同互补作用有关,提示了在临床实际工作中可能通过检测上述指标表达水平,继而达到预测患者预后的目的。

综上所述,脊柱骨折合并 SCI 患者血清 Neuritin、NFL、S100B 蛋白水平呈明显升高,且水平越高预后越差。然而,本研究尚且存在一定的不足之处:如本研究纳入对象年龄跨度相对较大,且未对不同病因患者进行对比分析,可能导致研究结果发生偏移。因此,在今后的研究过程中应开展多中心对照试验,以获取更为准确的数据。

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(上接第 4255 页)

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