·脑损伤与脑死亡评估·

诱发电位预测重症脑卒中患者不良预后时机研究

肖淑英 宿英英 张艳 赵红 庞英 刘祎菲

【摘要】 **目的** 探讨短潜伏期体感诱发电位(SLSEP)和脑干听觉诱发电位(BAEP)预测急性重症脑卒中患者预后的最佳时机。**方法** 以Glasgow昏迷量表(GCS)评分≤12分并经头部CT和(或)MRI检查证实的幕上大面积梗死或大容积出血患者作为观察对象,分别于发病后第1~3和4~7天行GCS评分、SLSEP和BAEP检查;并于发病后6个月采用改良Rankin量表(mRS)评估预后,分析发病后不同时间窗预测指标(GCS评分、SLSEP和BAEP)与预后评估指标(mRS评分)之间的关联性和预测准确性。**结果** (1)关联性分析:发病第1~3天,GCS评分、SLSEP和BAEP与mRS评分之间无关联性(均$P>0.05$);发病第4~7天,SLSEP和BAEP与mRS之间存在关联性(均$P<0.01$,$C>0.400$)。(2)预后预测准确性分析:发病第4~7天,SLSEP和BAEP Ⅴ波预测灵敏度为85.71%~97.62%、BAEP特异度为80.00%~90.00%,各项预测指标阳性预测值达89.13%~96.88%、SLSEP阴性预测值为83.33%~85.71%,其中SLSEP和BAEP预测准确度均达临床预期,尤以SLSEP最佳(88.46%~90.38%)。**结论** 急性重症脑卒中患者发病第4~7天SLSEP和BAEP预测不良预后的准确性较高。

【关键词】 卒中; 诱发电位,躯体感觉; 诱发电位,听觉,脑干; 预后; 敏感性与特异性

Timing of evoked potentials forecasting the prognosis of severe stroke patients

XIAO Shu-ying, SU Ying-ying, ZHANG Yan, ZHAO Hong, PANG Ying, LIU Yi-fei
Neurocritical Care Unit, Xuanwu Hospital, Capital Medical University, Beijing 100053, China
Corresponding author: SU Ying-ying (Email: tangsuyingying@sina.com)

【**Abstract**】 **Objective** To investigate the best assessment time of short-latency somatosensory-evoked potential (SLSEP) and brain stem auditory-evoked potential (BAEP) in predicting the prognosis of patients with acute severe stroke. **Methods** Fifty-two patients who were diagnosed as supratentorial massive cerebral infarction or large-volume cerebral hemorrhage by brain CT and/or MRI examination with Glasgow Coma Scale (GCS) ≤ 12 were selected as observation subjects. GCS, SLSEP and BAEP were recorded at 1–3 and 4–7 d after onset. Outcomes were examined 6 months later using the modified Rankin Scale (mRS). A mRS score of 0–4 was considered as favorable outcome while a score of 5–6 was considered as unfavorable. The correlation between different predictive indexes (GCS, SLSEP and BAEP) and outcome (mRS) was analyzed. The predictive accuracy was also analyzed. **Results** At 1–3 d after onset, there was no correlation between all the predictors and outcome ($P>0.05$, for all). At 4–7 d after onset, SLSEP and BAEP were significantly correlated with mRS ($P<0.01$, for all; $C>0.400$). At 4–7 d after onset, the prognostic sensitivity of SLSEP and BAEP Ⅴ wave was 85.71%–97.62%; prognostic specificity of BAEP was 80.00%–90.00%; positive predictive value of all predictors was 89.13%–96.88%; negative predictive value of SLSEP was 83.33%–85.71%; total predictive accuracy of SLSEP was 88.46%–90.38%. The predictive accuracy of both SLSEP and BAEP achieved the clinical expectation, and the former is better than the latter. **Conclusions** SLSEP and BAEP have a high accuracy rate in predicting the unfavorable prognosis of patients with acute severe stroke 4–7 d after onset.

【**Key words**】 Stroke; Evoked potentials, somatosensory; Evoked potentials, auditory, brain stem; Prognosis; Sensitivity and specificity

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作者单位:100053 北京,首都医科大学宣武医院神经内科重症监护病房

通讯作者:宿英英(Email:tangsuyingying@sina.com)

大量临床研究结果业已证实，诱发电位（EP）对脑卒中患者的预后可能具有一定预测作用[1-2]，但有关预测时间窗的选择尚存有争议。早期研究对预测时间窗的设置为发病后24小时或1～30天不等（第1～7、10～15、30天），甚至有学者认为可以发病后3个月作为预测时间窗[3-5]。然而，随着脑卒中治疗方法的进步，临床医师更加关注患者预后和（或）结局，希望通过有效的预后预测方法和治疗策略以提高患者生活质量。我们的前期研究发现，脑卒中发病7天内诱发电位与预后的关联性和一致性最佳，尤以上肢短潜伏期体感诱发电位（SLSEP）N20和Haupt分级[6]、脑干听觉诱发电位（BAEP）Ⅴ波和Hall分级[7]为最佳预测指标[1,8]。但笔者认为，仅以脑卒中发病第1～7天诱发电位作为预后预测指标的准确性尚不尽如人意，有必要进一步探索最佳预测时机，以为临床治疗提供更大帮助。本研究根据脑卒中病理生理学特点，以诱发电位参数和分级标准为评估指标，分别于病程早期（第1～3天）和迅速进展期（第4～7天）进行预后预测研究，以明确脑卒中后最佳预测时间窗，为临床制定有效治疗方案和提高患者生活质量提供依据。

对象与方法

一、研究对象

1. 纳入与排除标准 （1）年龄18～85岁。（2）发病时间 ≤ 7 d。（3）Glasgow昏迷量表（GCS）评分 ≤ 12分。（4）脑卒中诊断符合1996年中华神经科学会和中华神经外科学会联合制定的各类脑血管病诊断要点，并经头部CT和（或）MRI检查证实，其中缺血性卒中为幕上大面积（至少2/3大脑中动脉供血区域）梗死、出血性卒中为大容积（≥25 ml）血肿。（5）有以下情况者不在本研究观察范畴：发病前即存在听力障碍、影响诱发电位结果的脑部病变（小脑或脑干独立病变）、耳源性疾病或周围神经疾病、正在接受特殊药物治疗（如镇静药、麻醉药或肌肉松弛药等），以及存在影响预后的合并症（如严重心、肝、肾疾病或肿瘤等）。（6）本研究经首都医科大学宣武医院道德伦理委员会审核批准，患者及其家属知情同意并签署知情同意书。

2. 一般资料 选择2004年9月–2008年4月在我院神经内科重症监护病房住院治疗且符合病例纳入与排除标准的急性重症脑卒中患者共52例，男性28例，女性24例；年龄39～87岁，平均为（65 ± 13）岁；病变部位均为幕上，其中脑梗死33例、脑出血19例；预后良好者10例、预后不良42例。

二、研究方法

1. 前瞻性盲法研究 患者发病后第1～3和4～7天分别由神经内科重监护病房医师进行GCS评分，以及SLSEP和BAEP检测；发病后6个月进行预后评估，参与预后评估的医师不知晓临床评估和诱发电位检测结果。

2. 预后预测指标 （1）GCS评分：包括睁眼反应（1～4分）、言语反应（1～5分）和运动反应（1～6分）共3项内容15分。（2）SLSEP检查：检测设备为美国Nicolet公司提供的Viking Ⅳ-D型肌电图/诱发电位仪。患者仰卧位，刺激电极置于腕横纹上2～3 cm，记录电极分别置于对侧C_3或C_4后2 cm处旁开7 cm（C'_c）、C_6棘突（C_v6）和刺激同侧Erb点（CL_i），参考电极置于前额正中部（FPz）、刺激对侧Erb点（CL_c），接地电极置于刺激侧前臂。刺激参数：频率4.70 Hz、带通30～3000 Hz，放大器灵敏度100 μV、显示器灵敏度1 μV；每次刺激平均叠加500～1000次，分析时间50 ms，每次平均叠加300次，至少重复2次，以保证曲线重复度良好。以双侧N20波幅 ≥ 0.30 μV为N20存在、< 0.30 μV为消失。分级标准采用Haupt分级[6]，1级，潜伏期和波幅正常；2级，单侧或双侧潜伏期或波幅异常；3级，单侧反应减弱或消失；4级，双侧反应减弱或消失（对较差的一侧进行分级）。（3）BAEP检查：检测设备同SLSEP。记录电极置于颅顶中央部（Cz），参考电极置于声刺激同侧乳突（M1、M2），接地电极置于前额正中部（Fz）。经酒精棉球脱脂后将电极置于上述部位，皮肤电极阻抗 < 5 kΩ。患者仰卧位，插入式耳机一侧耳输入短声刺激为11.10 Hz、刺激强度90 dB，对侧耳以40 dB白噪声遮蔽；带通80～3000 Hz、灵敏度25或50 μV，每次平均叠加1000～2000次，分析时间10 ms，每耳每次至少重复检测2次，以保证曲线重复度良好。所有患者Ⅰ波存在，以Ⅴ波正常、分化不良或消失为判断标准[1]，采用Hall分级[7]，1级，正常；2级，轻度异常[Ⅰ～Ⅴ波分化良好但存在以下任意一种情况，即Ⅰ、Ⅲ和（或）Ⅴ波峰潜伏期（PL）延长，Ⅰ～Ⅲ、Ⅲ～Ⅴ和（或）Ⅰ～Ⅴ波峰间潜伏期（IPL）延长，Ⅲ～Ⅴ/Ⅰ～Ⅲ波峰间潜伏期 > 1，Ⅴ/Ⅰ波波幅 < 0.50]；3级，中度异常，即Ⅲ和（或）Ⅴ波分化不良、重复性差或Ⅴ波消失；4级，重度异常，即仅存在Ⅰ波或所有波均消失（对较差的一侧进行分级）。

表1 预测指标与预后评估指标之间的关联性分析[例(%)]

Table 1. The correlation analysis between predictive indexes and prognostic markers [case (%)]

Predictive index	Onset for 1–3 d						Predictive index	Onset for 4–7 d					
	N	Favorable outcome	Unfavorable outcome	χ^2 value	*P* value	*C* value		N	Favorable outcome	Unfavorable outcome	χ^2 value	*P* value	*C* value
GCS (score)				0.495	0.482	—	GCS (score)				3.684	0.055	—
9–12	26	6 (23.08)	20 (76.92)				9–12	20	7 (35.00)	13 (65.00)			
3–8	26	4 (15.38)	22 (84.62)				3–8	32	3 (9.38)	29 (90.63)			
SLSEP				0.000	1.000	—	SLSEP				18.338	0.000	0.511
N20	9	2 (22.22)	7 (77.78)				N20	7	6 (85.71)	1 (14.29)			
N20 disappeared*	43	8 (18.60)	35 (81.40)				N20 disappeared*	45	4 (8.89)	41 (91.11)			
Haupt grade				0.000	1.000	—	Haupt grade				13.581	0.000	0.455
1–2	9	2 (22.22)	7 (77.78)				1–2	6	5 (83.33)	1 (16.67)			
3–4	43	8 (18.60)	35 (81.40)				3–4	46	5 (10.87)	41 (89.13)			
BAEP				0.047	0.828	—	BAEP				14.545	0.000	0.468
Ⅴ	27	6 (22.22)	21 (77.78)				Ⅴ	14	8 (57.14)	6 (42.86)			
Ⅴ disappeared#	25	4 (16.00)	21 (84.00)				Ⅴ disappeared#	38	2 (5.26)	36 (94.74)			
Hall grade				0.063	0.802	—	Hall grade				11.329	0.001	0.423
1–2	32	7 (21.88)	25 (78.13)				1–2	20	9 (45.00)	11 (55.00)			
3–4	20	3 (15.00)	17 (85.00)				3–4	32	1 (3.12)	31 (96.88)			

*at least one side disappeared; #at least one side disappeared。GCS, Glasgow Coma Scale, Glasgow 昏迷量表; SLSEP, short-latency somatosensory-evoked potential, 短潜伏期体感诱发电位; BAEP, brain stem auditory-evoked potential, 脑干听觉诱发电位。The same for tables below

3. 预后评价指标 根据改良Rankin量表(mRS)分为7级[9]:0分,无症状;1分,有神经功能缺损症状与体征,但无明显残疾;2分,轻残;3分,中残;4分,中等重残;5分,重残并卧床;6分,死亡。mRS评分0~4分为预后良好,5~6分为预后不良。

4. 统计分析方法 采用SPSS 11.5统计软件进行数据处理与分析。预测指标与预后评估指标的关联性分析采用χ^2检验,以$P \leqslant 0.05$为预测指标与预后评估指标之间存在关联性,并计算各指标间的Pearson列联系数(C),以$C < 0.400$为低度关联、0.400~为中度关联、0.700~为高度关联[10]。对预测不良预后指标(GCS评分3~8分、SLSEP任意一侧N20消失、BAEP任意一侧Ⅴ波分化不良或消失、SLSEP Haupt分级和BAEP Hall分级均达3~4级)行准确性分析(包括敏感性、特异性、阳性预测值、阴性预测值和准确性),以≥80%为理想水平[11]。

结 果

一、诱发电位预测准确性分析

1. 发病第1~3天 GCS评分、SLSEP和BAEP各项预测指标与预后评估指标(mRS评分)之间无关联性(均$P > 0.05$,表1)。各项预测指标中,以SLSEP灵敏度较高(83.33%)但特异度较低(20.00%);虽然各项指标阳性预测值均较高,但阴性预测值均较低,预测准确度未达到临床预期(45.15%~71.15%,表2)。

2. 发病第4~7天 除GCS评分外,SLSEP和BAEP各项预测指标均与预后评估指标(mRS评分)之间存在关联性,Pearson列联系数达中度关联性(表1)。SLSEP和BAEP Ⅴ波分化不良或消失预测灵敏度达85.71%~97.62%,BAEP Hall分级3~4级预测特异度为90.00%,SLSEP和BAEP阳性预测值达89.13%~96.88%,SLSEP阴性预测值为83.33%~85.71%,除GCS评分和BAEP Hall分级外,其余各项指标预测准确度均达到临床预期效果(84.62%~90.38%,表2)。

二、发病后各项预测指标的变化

1. GCS评分变化 本组52例患者中13例发病第1~7天时GCS评分呈现出不同变化,其中评分恶化者(9~12分变为3~8分)9例(预后不良8例、良好1例),评分好转者(3~8分变为9~12分)4例(预后不良2例、预后良好2例,表3)。

表2 发病后不同时间窗各项预测指标对预后的预测结果(%)

Table 2. The predicting results for outcome of predictive indexes at 1–3 and 4–7 d after onset (%)

Predictive index	Sensitivity	Specificity	Positive predictive value	Negative predictive value	Accuracy rate
GCS 3–8					
1–3 d	52.38	60.00	84.62	23.08	53.85
4–7 d	69.05	70.00	90.63	35.00	69.23
N20 existed or disappeared					
1–3 d	83.33	20.00	81.40	22.22	71.15
4–7 d	97.62	60.00	91.11	85.71	90.38
SLSEP Haupt grade					
1–3 d	83.33	20.00	81.40	22.22	71.15
4–7 d	97.62	50.00	89.13	83.33	88.46
Differentiation of Ⅴ wave					
1–3 d	50.00	60.00	84.00	22.22	51.92
4–7 d	85.71	80.00	94.74	57.14	84.62
BAEP Hall grade					
1–3 d	40.48	70.00	85.00	21.88	45.15
4–7 d	73.81	90.00	96.88	45.00	76.92

表3 发病后不同时间窗预测指标的变化[例(%)]

Table 3. Change of predictive indexes at 1–3 and 4–7 d after onset [case (%)]

Predictive index	N	Favorable outcome	Unfavorable outcome
GCS (score)			
From 9–12 to 3–8	9	1 (1/9)	8 (8/9)
From 3–8 to 9–12	4	2 (2/4)	2 (2/4)
SLSEP			
N20*			
Recovered	4	4 (4/4)	0 (0/4)
Disappeared	25	0 (0.00)	25 (100.00)
Haupt grade			
From 1–2 to 3–4	25	0 (0.00)	25 (100.00)
From 3–4 to 1–2	5	5 (5/5)	0 (0/5)
BAEP			
Ⅴ wave#			
Disappeared or poorly differentiated	22	0 (0.00)	22 (100.00)
Recovered and well-differentiated	4	3 (3/4)	1 (1/4)
Hall grade			
From 1–2 to 3–4	22	1 (4.55)	21 (95.45)
From 3–4 to 1–2	7	5 (5/7)	2 (2/7)

*at least one side of N20 recovered or disappeared; #at least one side of Ⅴ wave had changes

2. 诱发电位变化 (1)SLSEP:52例中29例(55.77%)SLSEP呈现不同变化,其中单侧N20或双侧均消失25例,均预后不良;单侧或双侧恢复4例,均预后良好。Haupt分级变化者30例占57.69%,其中25例由1~2级升至3~4级,均预后不良;5例由3~4级降至1~2级,均预后良好。(2)BAEP:52例中26例(50%)呈现出不同Ⅴ波变化,其中22例单侧或双侧Ⅴ波消失或分化不良,均预后不良;4例单侧或双侧Ⅴ波恢复并分化良好(1例预后不良、3例预后良好)。Hall分级变化者29例占55.77%,其中22例Hall分级由1~2级升至3~4级(21例预后不良、1例预后良好);7例Hall分级由3~4级降至1~2级(2例预后不良、5例预后良好,表3)。

讨 论

利用诱发电位预测急性重症脑卒中患者预后的临床实践已经许多研究证实,但对其早期预测的最佳时机尚未取得共识。临床观察显示,幕上大面积梗死或大容积出血患者在发病急性期易出现病情加重现象,其中大多数患者预后不良[12-13]。鉴于此,我们选择发病第1~7天时对患者预后进行客观判断,有利于医疗决策和制定治疗方案。在本研究中,我们对幕上大面积梗死和大容积出血患者发病1~7天不同时间段的诱发电位进行临床观察,结果显示:发病第1~3天时,诱发电位预测指标(SLSEP和BAEP)与预后评估指标(mRS评分)之间无关联性,对不良预后的预测准确度较低;至发病第4~7天,预测指标与预后评估指标之间有关联性,其中SLSEP预测灵敏度高达97.62%、BAEP阳性预测值为94.74%~96.88%,SLSEP和BAEP Ⅴ波预测准确度均>80%,达到临床预期。有研究表明,双侧N20消失预测不良预后的特异度和阳性预测值均可达100%,与我们的前期研究结果相一致[14],单侧N20消失的阳性预测值为80%。本研究所纳入的缺血性卒中患者均表现为2个脑叶或2/3大脑中动脉供血区域梗死,出血性卒中为幕上大容积出血,未发现不同受累脑叶与预后的关联性,梗死灶或继发于其周围的脑水肿、脑疝所致脑组织移位和压迫等常导致梗死灶同侧和对侧神经传导通路破坏,引起双侧N20异常或消失,

预后不良。上述研究和本研究观察结果均提示，诱发电位的预测可信度优于GCS评分。由此可见，诱发电位预测重症脑卒中患者预后的时间窗可能与心肺复苏后昏迷患者不同，于脑卒中发病第4～7天时行诱发电位检测可更理想地预测预后，而心肺复苏后昏迷患者SLSEP预测时间窗为发病后3天内，其双侧N20消失预测不良预后的假阳性率仅0～0.70%[15]。

本研究结果显示，发病第4～7天时，BAEP预测幕上重症脑卒中患者不良预后的阳性预测值为94.74%～96.88%，高于SLSEP（89.13%～91.11%）和GCS评分（90.63%）。本组52例患者中15例（28.85%）表现为单侧Ⅴ波分化不良或消失，13例预后不良；23例（44.23%）表现为双侧Ⅴ波分化不良或消失，均预后不良，提示Ⅴ波分化不良或消失可以作为预测幕上重症脑卒中患者不良预后可信度较高的指标，且双侧异常较单侧异常的准确性更高，此与Liu等[16]预测自发性丘脑出血不良预后的研究结论相似。脑卒中患者BAEP Ⅴ波能够较好地反映脑干功能受损程度，幕上病变无论是原发病灶还是继发性脑水肿均可向下累及中脑，影响起源于中脑下丘的Ⅴ波，因此BAEP亦可用于预测幕上重症脑卒中患者预后。

本研究结果显示，幕上重症脑卒中患者发病第4～7天时，SLSEP预测不良预后的阳性预测值为89.13%～91.11%，仅次于BAEP；52例中20例（38.46%）呈现单侧N20消失，16例预后不良，25例（48.08%）双侧N20消失，均预后不良。N20起源于皮质和皮质下较大区域，唯有大量神经元缺失和（或）轴索破坏时才表现为完全消失。因此，双侧N20消失提示同侧病灶累及对侧，双侧大脑皮质功能广泛受损，预示患者可能预后不良。有研究显示，凡幕上卒中患者表现为双侧N20消失时，95%死亡、5%呈植物状态生存，仅极少数可部分恢复神经功能[17-18]。对本组患者的两次动态分析可见，脑卒中发病第4～7天时GCS评分降低且诱发电位（SLSEP和BAEP）表现不良者明显增加，其中以SLSEP和BAEP表现不良者居多占50%以上，且大多数预后不良。提示SLSEP和BAEP表现不良为病情不可逆转的信号，SLSEP N20单侧或双侧消失、BAEP Ⅴ波单侧或双侧分化不良或消失是所有预测指标中最为敏感和特异的指标，仅有极少数SLSEP和BAEP好转病例预后良好。SLSEP和BAEP对神经功能变化预测的准确性明显优于临床指标，本组有9例GCS评分恶化（9～12分变为3～8分）患者均预后不良、4例GCS评分好转（3～8分变为9～12分）患者中2例预后不良。值得注意的是，对于脑卒中发病第1～3天转归尚不明确的病例需加强SLSEP和BAEP动态评估，及时发现病情变化、调整医疗决策[19]。本研究所设定的脑卒中预后预测指标是在以往研究基础上筛选出来的诱发电位参数和分级标准（Haupt分级和Hall分级）[1]，与SLSEP N20和BAEP Ⅴ波相比，上述两项分级标准并未提高预测准确性，因此我们认为，幕上重症脑卒中患者不良预后预测指标应以SLSEP N20和BAEP Ⅴ波为参考依据。

总之，幕上重症脑卒中患者以发病第4～7天时为预测不良预后的敏感时间窗，SLSEP N20和BAEP Ⅴ波为最佳预测参数，与GCS评分相比，SLSEP和BAEP预测准确性更高。由于本研究样本量较小，尚待进一步扩大样本量以提高研究证据的临床指导意义。

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117th Meeting of the British Neuropathological Society

Time: March 2–4, 2016

Venue: Royal College of Physicians, London, UK

Website: http://www.bns.org.uk/next–meeting

The 117th Meeting of the British Neuropathological Society (BNS) will be held on March 2–4, 2016. The meeting will be held at the Royal College of Physicians with its excellent conference facilities and central London location. The meeting will be of interest to neuropathologists, neurologists and neuroscientists as it attracts a wide range of speakers from within the UK and abroad. Trainees in neuropathology and neurology are particularly encouraged to attend and it is expected that a training meeting will be arranged by neuropathology trainees on the morning of Wednesday prior to the start of the main meeting.

The symposium will brings together a number of internationally renowned scientists working in a field of interest in neuropathology. At the remainder of the meeting a range of original work will be presented in oral and poster formats covering many aspects of neuropathology and related neuroscience fields. Members of the BNS should take the opportunity to attend the Business Meeting of the Society and also the Professional Affairs Meeting. The annual review of cases from the External Quality Assurance scheme organized by the Society will take place and those who take part in this scheme are encouraged to participate in this process.

10th World Stroke Congress

Time: October 26–29, 2016

Venue: Hyderabad, India

Website: http://wsc.kenes.com

The 10th World Stroke Congress (WSC) promises to attract acclaimed experts in stroke from around the world. The congress will show a cutting-edge educational and scientific experience, focusing on the latest developments in stroke prevention, acute management and restorative care after stroke. There will be a particular emphasis on the issues related to stroke care in the South Asian region. Join WSC 2016 for 4 d of debates, discussions and collaborations in the exciting city of Hyderabad, India.