·论著·

# 107例脊髓亚急性联合变性患者的临床特征分析

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**摘要 目的：**探讨脊髓亚急性联合变性的临床、影像及电生理特征。**方法：**回顾性分析107例脊髓亚急性联合变性住院患者的临床资料，总结其临床、影像及电生理特点。**结果：**本组患者起病年龄从21~87岁，男性显著多于女性（*P*<0.05）。临床表现以行走不稳最多见（76.6%），其次为双下肢麻木和/或无力（47.7%），四肢麻木和/或无力排在第三位（26.2%）；伴随症状中头晕最多见（19.6%），尿便障碍（9.3%），也可有视力减退、反应迟钝等。巨幼细胞贫血较VitB12血清浓度降低检出率高（*P*=0.041），二者吻合度一般（*Kappa*=0.512）；同型半胱氨酸血浆浓度增高较巨幼细胞贫血意义更大（*P*=0.00），二者吻合度一般（*Kappa*=0.567）。脊髓及颅脑常规MRI阳性检出率56.1%，病变易发于脊髓C2～C7及T1～T4节段。神经电生理阳性检出率79.8%（75/94），其中脊髓病变合并周围神经病变47例，单纯周围神经病变25例。**结论：**脊髓亚急性联合变性临床表现复杂多样，血清VitB12浓度可能掩盖病情，而高同型半胱氨酸血浆浓度有更大的提示作用，二者的血液度变化同巨幼细胞贫血在疾病不同阶段时常不平行。

**关键词** 脊髓亚急性联合变性；临床特征；VitB12缺乏；高同型半胱氨酸；周围神经病变
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**Analysis of Clinical Characteristics in 107 Patients with Subacute Combined Degeneration of Spinal Cord** *LI Heng-yu, CHEN Hao, XU Kai, YE Xin-chun, DONG Li-guo, ZHANG Shen-yang, CUI Gui-yun. Department of Neurology, the Affiliated Hospital of Xuzhou Medical University, Jiangsu 221000, China*

**Abstract Objective:** To analyze the clinical, electrophysiological and imaging features of subacute combined degeneration of spinal cord. **Methods:** A retrospective study was performed on the clinical data of 107 inpatients with subacute combined degeneration of spinal cord in which clinical, electrophysiological, and imaging features were summed up and analyzed. **Results:** The age of onset was 21~87 years, and male patients significantly outnumber female patients (*P*<0.05). Instability in gait was the most common clinical manifestation (76.6%) followed by numbness and/or weakness in both lower limbs (47.7%) and numbness and/or weakness in the extremities (29.0%). Among the concomitant symptoms, the most common was dizziness (19.6%) followed by urinary disturbance (9.3%), and vision loss and decreased responsiveness were also observed. Detection rate of megaloblastic anemia was significantly higher than that of serum VitB12 concentration decrease (*P*=0.041), and the degree of coincidence was medium (*Kappa*=0.512). Increased serum homocysteine concentration yielded a more significantly higher detection rate than that of megaloblastic anemia (*P*=0.00); the degree of coincidence was medium (*Kappa*=0.567). The positive detection rate of MRI findings of the spinal cord and brain was 56.1%. The lesions were prone to occurring at the C2~C7 and T1~T4 segments of the spinal cord. Positive detection rate of electrophysiology was 79.8% (75/94), including 47 cases of spinal cord disease complicated with peripheral neuropathy and 25 cases with peripheral neuropathy alone. **Conclusion:** The clinical manifestations of subacute combined degeneration of spinal cord are complex. Serum vitamin B12 concentration may conceal the condition while a high level of homocysteine may offer a more significant role in detection; changes in blood concentration of both elements often do not parallel megaloblastic anemia at different stages of the disease.

**Key words** subacute combined degeneration of spinal cord; clinical features; VitB12 deficiency; hyperhomocysteinemia; peripheral neuropathy

脊髓亚急性联合变性（subacute combined degeneration of spinal cord，SCD）是维生素B12（Vitamin B12，VitB12）缺乏常见的神经系统并发症，其特征为感觉异常、深感觉障碍、痉挛性瘫痪或四肢麻痹。由于其临床症状表现复杂多样、辅助检查缺乏敏感性及特异性等，在临床工作中常被误诊、漏诊，病程超过6月预后不佳[1,2]，故正确诊断至关重要。本研究回顾性分析107例SCD患者的临床、生化学、影像及电生理方面表现，旨在为临床诊疗及时性提供进一步思路。

## 1 资料与方法

### 1.1 一般资料

收集自2010年11月至2016年11月徐州医科大学附属医院神经内科收治的107例SCD住院患者的临床资料，进行统计分析。诊断原则及标准参考Hemmer等[3]、Briani等[4]的研究。临床症状表现为行走不稳82例(76.6%)，双下肢麻木和/或无力51例(47.7%)，四肢麻木和/或无力31例(26.2%)，伴头晕21例(19.6%)，伴尿便障碍10例(9.3%)，伴视力减退4例(3.7%)，伴反应迟钝记忆力下降2例(1.9%)；神经系统阳性体征双侧肢体腱反射减弱或消失63例(58.9%)，深感觉障碍59例(55.1%)，对称性肢体肌力下降56例(52.3%)，双侧肌张力增高、腱反射活跃、巴氏征阳性46例(43.0%)，闭目难立45例(42.1%)，共济失调25例(23.4%)，对称性末梢型痛觉减退18例(16.8%)。

### 1.2 方法

统计患者的血液化验[血常规、血清VitB12浓度、血浆同型半胱氨酸(homocysteine，HCY)浓度]；常规MRI(包括头颅3.0T、颈椎1.5T、胸椎1.5T)；神经-肌电图检查[运动神经传导速度(motor nerve conduction velocity，MCV)、感觉神经传导速度(sensory nerve conduction velocity，SCV)、H反射、体感诱发电位(somatosensory evoked potential，SEP)]结果。排除2例血液化验结果不详(患者拒检)，105例患者完成血常规化验、85例同时完成血清维生素B12浓度测定、55例同时完成血浆HCY浓度测定(全部患者血样提取时间均在入院后、静脉补充甲钴胺治疗之前)。82例完成常规MRI检查。94例完成神经-肌电图检查。

### 1.3 统计学处理

应用SPSS 16.0统计学软件进行数据分析，计数资料采用$\chi^2$检验、*Fisher*确切概率检验、*u*检验及*k*检验。$P<0.05$为差异有统计学意义。$0.7>k\geq0.4$为吻合度一般，$k\geq0.7$为吻合度较强。

## 2 结果

### 2.1 发病人群特征

除外4例重复住院患者，男性占66.0%(68/103)，女性占34.0%(35/103)，男性患者多于女性，差异有统计学意义($U=3.252$，$P<0.05$)，男女发病比例约为2.2:1；发病年龄21~87岁，平均(59.64±12.67)岁，60~70岁为发病高峰。

### 2.2 病因分析

通过详细的病史询问，结合既往化验及检查结果，统计107例SCD患者病因，原因不明33.9%，消化系统疾病27.0%，长期素食17.4%，长期酗酒7.8%，贫血史6.1%，甲状腺疾病史3.5%，其他腹腔手术史2.6%，糖尿病1.7%。

### 2.3 实验室结果

巨幼细胞贫血者占74.3%(78/105)，维生素B12血清浓度降低者55.3%(47/85)，HCY血浆浓度增高69.1%(38/55)。统计发现巨幼细胞贫血较VitB12血浆浓度降低检出率高，二者吻合度一般；同时，HCY血浆浓度增高对无巨幼细胞性贫血患者有更大的意义，二者吻合度一般，见表1、2。

表1 VitB12血清浓度降低与巨细胞贫血阳性检出率

| 巨幼细胞贫血 | VitB12 | | 合计 |
|---|---|---|---|
| | 正常 | 降低 | |
| 无 | 23 | 5 | 28 |
| 存在 | 15 | 42 | 57 |

注：巨细胞性贫血较VitB12血清浓度降低检出率高($P=0.041$)，二者吻合度一般，*Kappa*=0.512

表2 HCY血清浓度增高与巨细胞贫血阳性检出率

| 巨幼细胞贫血 | HCY | | 合计 |
|---|---|---|---|
| | 正常 | 增高 | |
| 无 | 14 | 8 | 22 |
| 存在 | 3 | 30 | 33 |

注：血浆HCY浓度增高较巨细胞性贫血检出率高($P=0.00$)，二者吻合度一般，*Kappa*=0.567

### 2.4 影像结果

共有82例患者完成常规MRI(包括头颅3.0T、颈椎1.5T、胸椎1.5T)检查，病灶阳性检出率56.1%(46/82)，其中颅内出现病灶12例。病程≤6月者阳性率更高($P=0.015$)。髓内病灶自颈段至胸段全长范围内均可见(以脊髓后索及侧索受累为著，表现为$T_2$序列长信号，矢状面呈“条带状”或“斑片样”)，但统计后发现，病灶更多集中出现于$C_2$~$C_7$脊髓节段，其次为$T_1$~$T_4$节段，见图1。

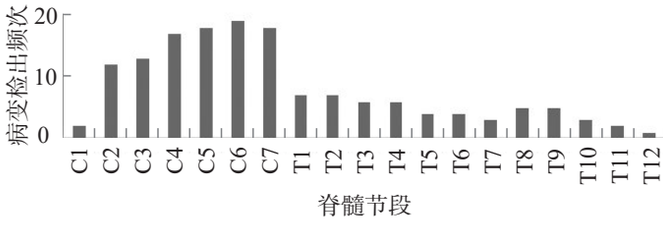



图1 脊髓颈胸段MRI病变检出率

### 2.5 电生理检查结果

共计94例患者完成电生理检查(EMG)，检测出异常指标75例(79.8%)。其中脊髓病变合并周围神经病变47例，单纯周围神经病变25例，2例SEP潜伏期延

长。周围神经病变检出率为74.7%。与运动神经相比，感觉神经更易受累（$P$=0.001），见表3。

表3 SCD患者EMG检查结果

| 检查项目 | 正常 | 异常 | 合计 |
|---|---|---|---|
| MCV | 62 | 32 | 94 |
| SCV | 39 | 55 | 94 |
| H反射 | 4 | 47 | 51 |
| SEP | 0 | 2 | 2 |

注：MCV异常特指传导速度减慢；SCV异常特指传导速度减慢；H反射异常特指潜伏期延长及未引出；SEP异常特指潜伏期延长

## 3 讨论

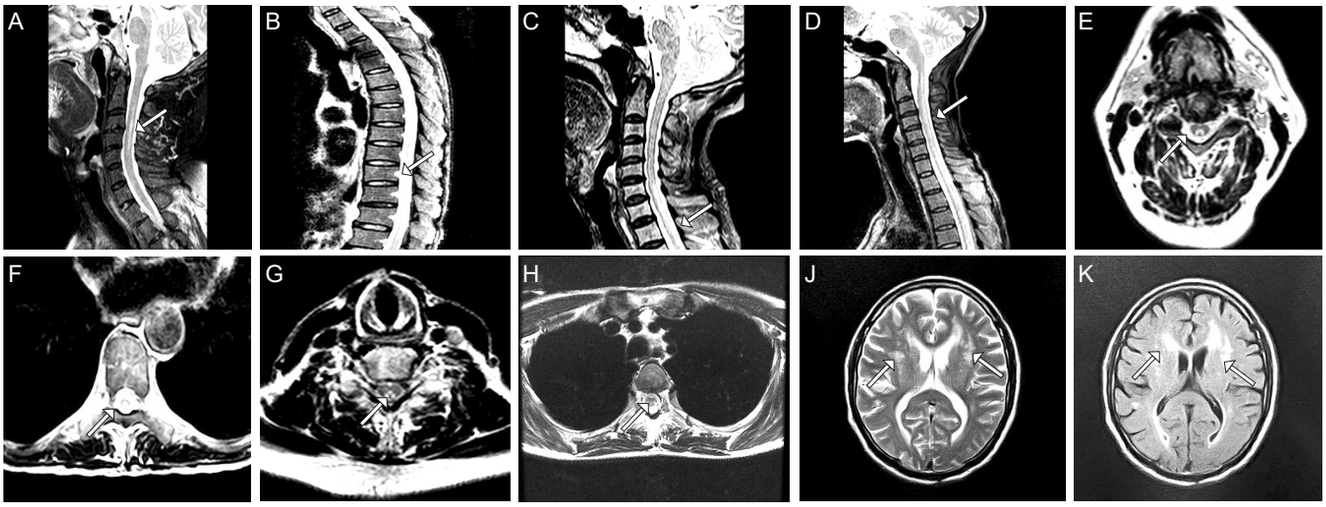
SCD是由于代谢因素所致的多系统（包括血液、胃肠、精神和神经）功能异常的一组临床综合征。神经症状可以孤立发生，包括运动障碍、感觉减退或缺失、平衡和反射异常及认知障碍，极端情况可致昏迷或精神疾病[5]。目前认为SCD可能的发病机制有以下几种：①VitB12缺乏：钴胺素在体内形成2种活性成分，甲钴胺和腺苷钴胺，二者分别以辅酶形式参与甲硫氨酸、琥珀酰-CoA的代谢，促进甲基传递链、髓磷脂合成、维护线粒体功能[4]。②VitB12代谢被干扰：甲钴胺和腺苷钴胺中心的三价钴还原为一价钴时方有活性作用（高度亲和性），$N_2O$极易与之反应还原成氮气和羟基，后者使蛋氨酸合成酶失活，致钴胺素包内代谢障碍[6]，从而引起中枢和外周神经系统功能障碍。此外，推测可能与自身免疫功能紊乱有关联，有报道统计高达45%的TPOAb阳性甲状腺功能减退症患者同时合并胃壁细胞抗体阳性[7]。

VitB12缺乏在60岁以上的西方人群中约占20%[8]，本组患者中60~70岁年龄组亦为发病高峰。据统计结果，本地区患者最多见病因是消化系统疾病，与近期文献报道[1,4]一致：包括慢性萎缩性胃炎、部分胃切除术及长期抗酸治疗等。其次为长期素食，人体内钴胺素主要来源自动物蛋白，包括肉类和蛋类[9]。长期酗酒排在第三位：酒精可致胃粘膜损伤、胃酸内因子分泌减少、酒精中毒等，VitB12吸收不良；且饮酒后常进食减少，VitB12摄入不足。既往尚缺乏流行病学关于发病性别差异的文献报道，本文发现男性发病率高于女性，但在消化系统疾病的病因差异无统计学意义（$P$>0.05），具体机制还需进一步研究。

目前对于VitB12缺乏欠缺理想的检测手段，虽血液及尿液化验是重要指标，但其易受诸多因素影响，如先天基因缺陷致代谢异常、肾功能不全、骨髓增生性疾病、院外钴胺素补充等。临床实践中，巨幼细胞性贫血是触发检查VitB12状态最常见的因素，但并非SCD患者均存在巨细胞贫血的血液学改变，据报道约20%患者不伴有贫血[8]。其次，钴胺素正常水平目前尚不完全清楚，有研究认为血清钴胺素<148 pmol/L（200 ng/L）对于VitB12缺乏症的诊断敏感性达97%[10]。本研究中，巨幼细胞贫血者占74.3%，VitB12血清浓度降低者为55.3%（本研究VitB12血清浓度<141 pmol/L为降低），与巨幼细胞贫血吻合度一般。VitB12缺乏的敏感性较低，分析存在以下可能性：检测例数较少，检测界值相对较高，部分患者存在亚临床缺乏，及外院已补充等。有研究认为目前临床检测的是总血清VitB12水平，其中仅小部分有活性且处于动态变化中，代谢性VitB12缺乏发生时，总血清VitB12水平仍可在正常范围内[11]。故血清钴胺素正常及低界水平也不能排除诊断。

血浆HCY水平在钴胺素缺乏的中早期即可增加[8]。本研究中，HCY血浆浓度增高者为69.1%，其增高对于无幼巨细胞贫血在临床诊断上有进一步指导意义；同样，二者检出率吻合度一般。这提示HCY代谢障碍与巨幼细胞贫血在钴胺素缺乏不同时期，并非平行，或者存在不匹配。近期，Huemer等[12]在关于钴胺素相关的再甲基化障碍疾病研究中提出，任何呈现神经和/或视觉和/或血液学异常症状、亚急性脊髓变性等组合的患者，建议测量血浆总HCY浓度。HCY是由甲硫氨酸（Methionine，Met）形成的氨基酸，其再甲基化是维持生物体甲基化能力并除去过量HCY的重要机制。机体内甲基化反应（包括DNA甲基化、肌酸和髓磷脂合成等）均由S-腺苷甲硫氨酸（SAM）作为甲基供体，任何Met-Hcy-SAM途径的紊乱可致甲基化能力下降并损害多个系统代谢过程[13,14]。钴胺素在体内的活性成分之一，甲基钴胺是甲硫氨酸合成酶的辅酶，催化甲基向同型半胱氨酸转移形成甲硫氨酸[15]，因此，钴胺素缺乏时，HCY水平升高具有高敏感性，对于疾病的临床诊断具有重要价值[8]。

SCD脊髓受累病理学特征包括多灶性脱髓鞘、空泡化及轴突变性，通常累及背侧索、外侧索，有时也累及前索，影像学上具有一定特征性的表现[16,17]，以脊髓后索及侧索受累为著，病灶自颈段至胸段全长范围均可见。颈/胸椎常规MRI表现为长$T_2$信号，矢状面呈“条带状”或“斑片样”；在横轴位特异性表现有所不同[18]，可呈“倒V”型、“圆点”型、“三角征”、“双目望远镜征”及“小”字征（图2）。本研究发现脊髓$C_2$~$C_7$及




注：A、B、C中病灶均位于脊髓后索，但横轴位表现多样：分别在E、F、G中呈“倒V”型、“圆点”型及“三角征”；D中病灶同时累及脊髓侧索，切面轴位图H中呈现“小”字征。J、K示两侧额叶、两侧基底节区多发斑片状、斑点状长$T_2$信号、flair高信号对称性白质脱髓鞘病灶

图2 SCD患者影像学表现

$T_1$~$T_4$节段易受累，与既往文献报道“颈椎及上段胸椎多发”相符合。另外本研究中14.6%的患者颅脑常规MRI发现病灶，主要表现为两侧额叶、基底节区、半卵圆中心多发对称斑片状白质脱髓鞘病灶，$T_2$WI及flair呈高信号，与既往报道相符合[4]。颅内上述区域白质纤维传导束密集，而胶质细胞、髓磷脂和间质是哺乳动物中枢神经系统主要受累结构，钴胺素缺乏可引起星形胶质细胞和小胶质细胞胶质纤维酸性蛋白沉积；在钴胺素缺陷型大鼠的研究中发现细胞因子和生长因子失衡：髓磷脂毒素细胞因子（主要是TNF-α）及髓磷脂毒素生长因子合成增多，而髓鞘营养细胞因子（IL-6）、髓鞘营养表皮生长因子的合成降低[19]。故推测，有髓神经纤维髓鞘合成障碍、破坏增多，是病灶产生的主要原因。

针对常规MRI协助诊断亚变的灵敏度，目前仍存分歧。有研究[17]认为$T_2$WI显示病灶异常增高信号灵敏度较高（52.8%）；另有研究[20]观察到其敏感性仅14.8%。本研究中，常规MRI病变阳性检出率为56.1%，尤其病程≤6月者更易发现病灶；随着病程的迁延，敏感性反而降低。此类文献报道较少，可能早期由于星形胶质细胞增生致组织含水量增加，因此MRI出现长$T_2$信号；而慢性期胶质增生、结构较为稳定，故无异常信号[21]。

神经-肌电图作为功能性检查在早期可能优于影像学检查，但其特异性较差。本研究中周围神经病变检出率较高，为74.7%，与运动神经相比，感觉神经更易受累。脊髓病变合并周围神经病变47例，单纯周围神经病变25例，提示周围神经损害与脊髓长传导束损害并非一致。有研究[22]认为胫骨SEP异常敏感性高，并且可有VEP P100潜伏期延长。故全面的神经电生理检查有助于评估潜在病变部位。

本研究可为SCD的诊断提供一定的临床依据，同时存在以下不足：甲基丙二酸水平增加是组织中VitB12缺乏的表现，在补充钴胺素治疗开始后数天后仍然存在[23]，是VitB12代谢功能不全具代表性的标志，但因其检测成本较高，本组患者均未采取。全转运谷氨酸素可能是VitB12消耗的最早标志物，可通过免疫测定，其水平降低对提示VitB12受损状态更可靠，但关于应用模式和截止值的分配仍然存在差异，目前临床上尚未广泛应用[24]。

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