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85 例多系统萎缩患者预后影响因素的分析*

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摘要 目的:探讨多系统萎缩(multiple system atrophy, MSA)患者预后的影响因素。**方法:**连续收集 2016 年 1 月到 2019 年 1 月空军军医大学第一附属医院神经内科住院及门诊收治的 85 名临床确诊 MSA 患者的临床资料,每隔 6 月对患者进行随访记录,直至需辅助行走时间,研究时限 3.5 年,筛选 10 个可能影响 MSA 独立行走的危险因素,应用 Cox 比例风险回归模型进行单因素及多因素回归分析。**结果:**85 例 MSA 患者中,很可能 MSA38 例(44.7%),可能 MSA47 例(55.3%),以帕金森表现(MSA-P)43 例(50.6%),以小脑性共济失调表现(MSA-C)42 例(49.4%),男性 46 例(54.1%),女性 39 例(45.9%),起病年龄 54.7 ± 8.8 岁,首发运动症状 30 例(35.3%),首发非运动症状 55 例(64.7%)。起病至非运动症状合并运动症状中位时程 27.9(11.5, 40.5)月。截至本研究终止,28 例(32.9%)患者独立行走,57 例(67.1%)患者不能独立行走,起病至辅助行走中位时程 36.0(22.5, 54.0)月。Cox 比例风险回归模型显示起病年龄大(HR=1.041, 95% CI 1.000-1.083, $P=0.049$)、H&Y 高分期(HR=2.015, 95% CI 1.031-3.938, $P=0.040$)、起病至非运动症状合并运动症状短时程(HR=0.980, 95% CI 0.967-0.993, $P=0.003$)是 MSA 患者发展至辅助行走状态的危险因素。**结论:**起病年龄大、H&Y 高分期、起病至非运动症状合并运动症状短时程是 MSA 患者辅助行走的不良预后因素。

关键词:多系统萎缩;辅助行走;预后;生存分析

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Analysis of Prognostic Factors in 85 Patients with Multiple System Atrophy*

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ABSTRACT Objective: To explore the relevant factors on the prognosis of patients with multiple system atrophy (MSA). **Methods:** The clinical data of 85 clinically diagnosed MSA patients admitted to the Department of Neurology, First Affiliated Hospital of Air Force Military Medical University was collected from January 2016 to January 2019. These MSA patients were followed up every 6 months until they needed aid to walk. The study time limit is 3.5 years. 10 factors that may affect independent walking of MSA patients were screened for survival analysis. These factors were studied by Cox proportional hazard regression model for univariate and multivariate regression analysis. **Results:** In this study, there were 38 cases of probable MSA patients (44.7%), 47 cases (55.3%) of possible MSA patients, 43 cases (50.6%) with Parkinson's disease-like symptoms (MSA-P), 42 cases (49.4%) with cerebellar syndrome (MSA-C). Among them, 46 patients (54.1%) were male, 39 patients (45.9%) were female, with onset age of 54.7 ± 8.8 years. 30 patients (35.3%) suffered from the onset of motor symptoms, 55 patients (64.7%) suffered from the onset of non-motor symptoms. The median time between onset of MSA and non-motor symptoms combined with motor symptoms was 27.9 (11.5, 40.5) months. As of the end of the study, 28 patients (32.9%) were able to walk independently, and 57 patients (67.1%) were unable to walk independently. The median time between onset of MSA and dependent ambulation was 36.0 (22.5, 54.0) months. The Cox proportional hazard regression model suggested an old age (HR=1.041, 95% CI 1.000 to 1.083, $P=0.049$), H&Y high-stage (HR=2.015, 95% CI 1.031 to 3.938, $P=0.040$), short duration from onset of MSA to non-motor symptoms combined with motor symptoms (HR=0.980, 95% CI 0.967 to 0.993, $P=0.003$) were independent risky factors for predicting the development of MSA patients to dependent ambulation. **Conclusions:** The old age, H&Y high-stage, short duration from onset of MSA to non-motor symptoms combined with motor symptoms are prognostic risk factors for MSA patients.

Key words: Multiple system atrophy; Dependent Ambulation; Prognosis; Survival analysis

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前言

多系统萎缩(multiple system atrophy, MSA)是一种散发性神经退行性疾病^[1],其特征为自主神经衰竭、帕金森综合征、小

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脑性共济失调、锥体束征的各种组合。目前,该病病因、病机仍然不清^[2,3],以主要的运动特征分为两种临床亚型:帕金森综合征(MSA-P)和小脑性共济失调(MSA-C)。早期与帕金森病等鉴别困难^[4],最终确诊需要病理学证据,临床诊断为“很可能MSA”和“可能的MSA”。该病尚无特异性治疗^[5],患者发病后平均存活6至10年^[6]。目前,MSA的预后研究多来自国外,而国内的研究较少,样本量较小,部分为回顾性研究^[7,8],且不同研究之间的结果尚存分歧^[9]。为进一步探讨该病的预后影响因素,本研究前瞻性收集85例MSA患者的临床资料,采用生存分析方法探索了影响MSA患者预后的危险因素。

1 对象与方法

1.1 研究对象

连续收集2016年1月-2019年1月在空军军医大学第一附属医院神经内科帕金森及运动障碍专病门诊及病房的MSA患者。入选标准:符合2008年Gilman等^[10]提出的可能及很可能MSA诊断标准;排除标准:①不愿配合随访;②严重认知功能障碍;③既往因脑卒中或其他原因遗留肢体偏瘫或影响肢体活动者。家属对本研究知情同意并签署知情同意书。本研究经空军军医大学第一附属医院医学伦理委员会批准同意执行。

1.2 研究方法

详细记录患者临床特征,包括:性别、起病年龄、分型、诊断分级、首发症状(运动、非运动)、入组时其他症状(喘鸣、睡眠呼吸暂停)、锥体束征、左旋多巴反应、起病至非运动症状合并运动症状时程、起病至辅助行走时程、起病至首诊时程及Hoehn-Yahr(H&Y)。首发症状定义为:患者或家属提供最早出现的运动症状或非运动症状。起病至非运动症状合并运动症状时程:首发症状至同时出现运动症状和非运动症状的时间,其中

运动症状包括帕金森或小脑症状,非运动症状包括泌尿系统功能障碍、体位性低血压、性功能障碍。左旋多巴有反应定义:患者自觉或家属观察运动症状改善率或左旋多巴冲击试验改善率 $>30\%$ ^[11]。每6月进行门诊或电话随访,用代表日常生活活动能力(activities of daily living, ADL)的第2个里程碑事件^[12],即辅助行走(使用手杖,助行器或同伴的手臂随时提供支撑)作为预后评估终点事件。为提高随访率,每位患者留3个联系电话。

1.3 统计学方法

采用SPSS23.0统计学软件进行统计分析。计量资料进行正态性检验,符合正态分布用 $(\bar{x} \pm s)$ 的方式表示,采用t检验,不符合正态分布以中位数(P25, P75)表示,采用Mann-Whitney U检验。计数资料用n(%)表示,采用 χ^2 检验。应用Cox比例风险回归模型进行单因素及多因素回归分析,协变量进入和剔除模型的检验水准分别为0.05和0.10。 $P<0.05$ 代表有统计学意义的差异。

2 结果

2.1 MSA患者的基线临床特征

本研究共纳入85例MSA患者,其中很可能MSA38例(44.7%),可能MSA47例(55.3%)。男性46例(54.1%),女性39例(45.9%),起病年龄 54.7 ± 8.8 岁,MSA-P43例(50.6%),MSA-C42例(49.4%)。首发运动症状30例(35.3%),首发非运动症状55例(64.7%),起病至非运动症状合并运动症状中位时程27.9(11.5, 40.5)月。截止研究结束,2例患者失访,可能与电话变更或不愿后续随访有关,作为删失数据纳入生存分析。28例(32.9%)独立行走,57例(67.1%)不能独立行走[47例(55.3%)需辅助行走,8例(9.4%)依赖轮椅,2例(2.4%)长期卧床]。起病至辅助行走中位时程36.0(22.5, 54.0)月。见表1。

表1 85例MSA患者的基线临床特征
Table 1 Baseline clinical features of 85 patients with MSA

Clinical features	Overall(n)	MSA-P(n)	MSA-C(n)	Test value	P value
Sub-type	85(100.0)	43(50.6)	42(49.4)		
Diagnostic certainty					
Possible	38(44.7)	21(48.8)	17(40.5)		
Probable	47(55.3)	22(51.2)	25(59.5)	0.601 ¹⁾	0.438
Sex					
Male	46(54.1)	23(53.5)	23(54.8)		
Female	39(45.9)	20(46.5)	19(45.2)	0.014 ¹⁾	0.906
Age at onset(years)	54.7 $\pm$ 8.8	56.0 $\pm$ 9.5	52.9 $\pm$ 6.4	1.771 ²⁾	0.080
Symptoms onset					
Motor	30(35.3)	15(34.9)	15(35.7)		
Non-motor	55(64.7)	28(65.1)	27(64.3)	0.006 ¹⁾	0.936
Symptoms when Study entry					
Stridor	9(10.6)	3(7.0)	6(14.3)	1.199 ¹⁾	0.679
Sleep apnea	15(17.6)	5(11.6)	10(23.8)	2.169 ¹⁾	0.141
Pyramid	52(61.2)	27(62.8)	25(59.5)	1.095 ¹⁾	0.757

Levodopa beneficial response					
Yes	31(36.5)	23(53.5)	8(19.0)		
No	54(63.5)	20(46.5)	34(81.0)	10.877 ¹⁾	0.001 ⁴⁾
H&Y					
Stage1-2	33(38.8)	23(53.5)	10(23.8)		
Stage3-5	52(61.2)	20(46.5)	32(76.2)	7.880 ¹⁾	0.005 ⁴⁾
Time from onset to appearance of concomitant non-motor and motor symptoms(months)	27.9(11.5,40.5)	18.0(11.3,40.5)	17.0(12.0,46.5)	0.411 ³⁾	0.681
Time from onset to dependent ambulation(months)	36.0(22.5,54.0)	36.5(24.0,64.5)	36.0(20.0,48.0)	0.585 ³⁾	0.559
Time from onset to the first clinical visit(months)	19.5(2.0,18.0)	12.0(2.0,24.0)	8.5(2.8,16.5)	0.557 ³⁾	0.577
Walk independently					
Yes	28(32.9)	15(34.9)	13(31.0)		
No	57(67.1)	28(65.1)	29(69.0)	0.149 ¹⁾	0.700

注: 1) χ^2 值; 2) t 值; 3) U 值; 4) $P < 0.05$; H&Y: Hoehn-Yahr。
Note: 1) χ^2 value; 2) t value; 3) U value; 4) $P < 0.05$; H&Y: Hoehn-Yahr.

2.2 影响 MSA 患者预后的生存分析结果
根据既往国内外相关研究, 将临床分型、性别、起病年龄、H&Y 分期、锥体束征、左旋多巴反应、首发非运动症状、起病至非运动症状合并运动症状时程、喘鸣、睡眠呼吸暂停 10 个变量纳入 Cox 比例风险回归模型进行单因素及多因素分析。多因素分析结果显示: 起病年龄大 (HR=1.041, 95 % CI 1.000-1.083, $P=0.049$)、H&Y 高分期 (HR=2.015, 95 % CI 1.031-3.938, $P=0.040$)、起病至非运动症状合并运动症状短时程 (HR=0.980, 95 % CI 0.967-0.993, $P=0.003$) 是影响 MSA 患者发展至辅助行走的危险因素。见表 2。

表 2 85 例 MSA 患者 COX 单因素及多因素回归分析
Table 2 Single factor and multivariate regression analysis of COX in 85 patients with MSA

	Univariate analysis		Multivariate analysis	
	P value	HR (95.0 % CI)	P value	HR (95.0 % CI)
Sub-type	0.404	1.249(0.741-2.104)	0.149	1.653(0.835-3.272)
Sex	0.203	0.713(0.423-1.201)	0.757	.905(0.482-1.701)
Age at onset	0.004 ¹⁾	1.044(1.014-1.075)	0.049 ¹⁾	1.041(1.000-1.083)
H&Y	0.002 ¹⁾	2.617(1.445-4.739)	0.040 ¹⁾	2.015(1.031-3.938)
Pyramid	0.256	1.378(0.793-2.397)	0.171	1.519(0.835-2.764)
Levodopa beneficial response	0.876	0.958(0.558-1.643)	0.720	1.119(0.604-2.074)
Non-motor symptoms onset	0.451	0.803(0.455-1.419)	0.706	1.130(0.599-2.131)
Time from onset to appearance of concomitant non-motor and motor symptoms	0.001 ¹⁾	0.980(0.969-0.992)	0.003 ¹⁾	0.980(0.967-0.993)
Stridor	0.498	1.301(0.608-2.784)	0.596	1.270(0.524-3.079)
Sleep apnea	0.825	1.081(0.544-2.148)	0.737	.871(0.388-1.955)

Note: ¹⁾ $P < 0.05$; H&Y: Hoehn-Yahr.

3 讨论

MSA 是一种以帕金森综合征、小脑性共济失调、自主神经功能紊乱和锥体束功能障碍为特征的 α - 突触核蛋白病^[13], 较帕金森病更早出现行动能力受限^[14], 包括失去独立行走能力、依赖轮椅和长期卧床。因此, 探讨 MSA 患者预后的影响因素十分有必要。MSA 患者中超过 50 % 以非运动症状起病^[15], 可以出现在运动症状前数月甚至数年^[16]。这些患者多首诊于泌尿外科、心内科等其他科室, 导致患者长时间误诊。本研究首发非运动

症状 55 例(64.7 %), 起病至非运动症状合并运动症状中位时程 27.9(11.5, 40.5)月, 起病至首诊中位时程 19.5(2.0, 18.0)月, 均显示早期 MSA 诊断困难^[17]。因此, 关注早期的非运动症状特征有助早期 MSA 诊断。
有关 MSA 患者预后影响因素的研究较少, 且结论不一致^[18], 主要原因可能有以下几方面: ① MSA 为罕见病, 许多研究样本量较小, 不同地域人群的临床分型有差异^[6,19,20], 且部分为回顾性研究, 要进行多中心大样本前瞻性研究较为困难; ② MSA 表现复杂涉及多器官及系统, 起病隐匿, 多数以非运动症状起病,

不易被患者重视,误诊率高^[21-23],导致起病时间不易确定;②最终确诊为病理诊断,临床缺乏特异的诊断方法,不同研究者对诊断标准的把握尺度不同;③研究中筛选的预后影响因素不同,混杂因素较多影响研究结论。日本大型研究显示从发病到需要帮助行走、对轮椅的依赖、卧床不起状态及死亡的中位数间隔分别为3年、5年、8年和9年^[22]。本研究时限为3.5年,28例(32.9%)独立行走,57例(67.1%)失去独立行走能力,起病至辅助行走中位时程36.0(22.5, 54.0)月。多因素分析结果显示起病年龄大、H&Y高分期、起病至非运动症状合并运动症状短时程是影响MSA患者发展至辅助行走的危险因素。

起病年龄对MSA预后影响的研究结论尚有分歧。Watanabe等^[12]对日本208例很可能MSA及22例病理确诊的MSA病例进行回顾性分析,平均发病年龄55.4岁,较大的起病年龄增加了ADL功能恶化和死亡的风险。Ben-Shlomo等^[24]对433例病理确诊的MSA病例进行meta分析,平均起病年龄54.2岁,起病年龄晚的MSA患者生存期短。然而,Low等人^[25]对175例很可能MSA患者的北美前瞻性研究显示,平均年龄为63.4岁,没有发现起病年龄与预后死亡相关。Tada等^[26]的研究也认为发病年龄与MSA预后无关。本研究平均起病年龄54.7岁,起病年龄大是影响MSA患者发展至辅助行走的危险因素。目前,起病年龄影响MSA预后的机制不明,有待病理学进一步研究。

大多数研究显示起病至非运动症状合并运动症状时程越短,MSA预后越差。Watanabe等人^[12]表明MSA从初始症状到运动症状和自主神经功能障碍合并出现的中位时间为2年,起病后第2、4和6年出现运动症状和自主神经功能障碍合并症状的频率分别为57.4%、83.5%和96.5%,起病至运动症状和自主神经功能障碍合并出现的时程越短,ADL功能进展和死亡越快。王志伟^[7]等对国内123例MSA患者进行回顾性研究,从起病到运动和自主功能障碍合并出现的时间越短,特别是<3年时,进展为ADL各里程碑事件的速度越快。起病至非运动症状合并运动症状时程越短,可能表明 α -突触核蛋白的广泛积累范围越广泛,涉及器官系统损害越多^[27,28]。本研究显示起病至非运动症状和运动症状合并出现的中位时程27.9月,起病至非运动症状和运动症状合并出现时间越短,患者发展至辅助行走越快。

H&Y是反映运动症状累及范围和程度的重要标志之一,随着MSA的进展,H&Y会逐渐恶化。Seppi等人^[29]的一项前瞻性研究显示H&Y恶化程度为每年27.6%。Krim等^[30]对法国19例可能MSA及67例很可能MSA患者进行回顾性研究,入组时73.2%的患者H&Y为1或2期,5年后仅12.8%的患者H&Y为1或2期,83.7%的患者 $\geq$ 3期,高H&Y分期是MSA不良预后的危险因素。Wenning等^[31]对100例可能的MSA研究显示超过50%的患者起病5年内H&Y $\geq$ 4期,起病与辅助行走之间的平均时间为3年,低H&Y分期总病程更长。本研究时限为3.5年,61.2%的患者H&Y $\geq$ 3期,H&Y高分期是影响MSA患者发展至辅助行走的危险因素。

还有一些因素可能是影响MSA进展和存活的风险因素,包括临床分型、锥体束征、性别、喘鸣、首发非运动症状、睡眠呼吸暂停^[26],但结论上存在争议^[12]。本研究仅提示起病年龄大、

H&Y高分期、起病至非运动症状合并运动症状短时程,是预测MSA患者病情进展的危险因素。由于样本来自单个三甲医院,且样本量少,下一步应进行大样本、前瞻性、多中心的队列研究,尽可能考虑到各方面因素,尤其要重视患者早期的非运动症状,才能得出客观可靠的结论。

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