doi: 10.13241/j.cnki.pmb.2018.20.043

加兰他敏联合复方海蛇胶囊治疗阿尔茨海默病早发型痴呆的临床疗效及对血清 IL-6、IL-8、TNF-α 水平的影响 *

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摘要 目的:观察加兰他敏联合复方海蛇胶囊治疗阿尔茨海默病早发型痴呆的临床效果及对血清白细胞介素 -6、8(IL-6、IL-8)和肿瘤坏死因子 -α(TNF-α)水平的影响。**方法:**选择我院 2014 年 9 月 ~2016 年 9 月收治的 96 例阿尔茨海默病早发型痴呆患者,按照治疗方式分为对照组和实验组,每组 48 例。对照组予以加兰他敏治疗,实验组在对照组基础上加用复方海蛇胶囊治疗,观察和比较两组的临床疗效, 治疗前后血清 IL-6、IL-8、TNF-α、游离三碘甲状腺原氨酸 (FT_3)、游离甲状腺素 (FT_4)、简易智力状态评分(MMSE)、老年痴呆患者生活质量量表(QOL-AD)的变化以及不良反应的发生情况。**结果:**治疗后,实验组有效率显著高于对照组[93.75% vs 77.08%](*P<0.05*)。治疗前,两组血清 IL-6、IL-8、TNF-α、FT_3、FT_4、MMSE、QOL-AD 比较差异无统计学意义(*P>0.05*);治疗后,两组血清 IL-6、IL-8、TNF-α 水平均较治疗前显著降低,且实验组低于对照组(*P<0.05*);两组 FT3、FT4、MMSE、QOL-AD 均较治疗前明显上升,且实验组显著高于对照组(*P<0.05*)。两组不良反应的发生情况比较差异无统计学意义(*P>0.05*)。**结论:**加兰他敏联合复方海蛇胶囊治疗阿尔茨海默病早发型痴呆的临床效果优于加兰他敏单药治疗, 其能够降低患者血清 IL-6、IL-8 及 TNF-α 浓度,并能提高血清甲状腺激素的水平。

关键词:阿尔茨海默病早发型痴呆;加兰他敏;复方海蛇胶囊;炎症因子

中图分类号:R741.02;R749.16 **文献标识码:**A **文章编号:**1673-6273(2018)20-3988-04

Clinical Efficacy of Galantamine combined with Fufang Haishe Capsule in the Treatment of Early-Onset Alzheimer's Disease Dementia and the Effect on the Serum IL-6, IL-8, TNF-α Levels

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ABSTRACT Objective: To observe the clinical efficacy of galantamine combined with fufang haishe capsule in the treatment of early-onset Alzheimer's disease dementia and the effect on the serum interleukin - 6, 8 (IL-6, IL-8), tumor necrosis factor-α(TNF-α) levels. **Methods:** 96 cases of patients with early-onset alzheimer's disease dementia from September 2014 to September 2016 were selected and divided into the control group and the experimental group according to the treatment. The control group was treated by galantamine, while the experimental group (n=48) was treated on the by Fufang Haishe capsule based on the control group. The clinical curative effect, changes of serum levels of IL-6, IL-8, TNF-α, free three iodine thyroid original glycine (FT3) and free thyroxine (FT4), marks,mini-mental state examination (MMSE), alzheimer's patients quality of life scale (QOL-AD) before and after treatment and the occurrence of adverse reactions were observed and compared between two groups. **Results:** After treatment, the effective rate of experimental group was significantly higher than that of the control group [93.75% vs 77.08%] (*P<0.05*); the serum levels of IL-6, IL-8, TNF-α of both groups were significantly reduced than those before treatment, which were obviously lower than those of the control group (*P<0.05*); the FT3, FT4, MMSE, QOL-AD of both groups were significantly rised than before treatment, which were significantly higher in the experimental group were significantly higher than those of the control group (*P<0.05*). No significant difference was found in the occurrence of adverse reactions between two groups(*P>0.05*). **Conclusion:** Galantamine combined with Fufang Haishe capsule was more effective than those of galantamine monotherapy, in the treatment of early-onset alzheimer's disease dementia, it could reduce the serum levels of IL-6, IL-8 and TNF-α, and improve the levels of serum thyroid hormones.

Key words: Early-onset alzheimer's disease dementia; Galantamine; Fufang Haishe capsule; Inflammatory cytokines

Chinese Library Classification(CLC): R741.02; R749.16 Document code: A

Article ID: 1673-6273(2018)20-3988-04

* 基金项目:湖南省科技厅科研基金项目(2011SK3137)

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(收稿日期:2018-01-30 接受日期:2018-02-26)

前言

阿尔茨海默病早发型痴呆为神经系统的常见退行性疾病，发病隐匿，病程多呈进行性、慢性发展，表现为渐进性的认知功能、记忆及语言障碍，人格改变等是其主要临床表现，严重影响患者的生活质量[1,2]。目前，阿尔茨海默病早发型痴呆发病机制尚未完全明确，多与遗传因素、吸烟、脑外伤、文化程度低等因素相关，同时免疫炎症反应在其发病中发挥关键作用[3]。既往临床多采用抗胆碱酯酶抑制药物治疗，其中加兰他敏是其代表药物，能够延缓疾病的进程，且耐受性较好，但临床效果并不确切[4,5]。现代研究显示阿尔茨海默病早发型痴呆患者于常规西医治疗基础上联合中医疗法能够增加临床疗效，复方海蛇胶囊作为一种纯天然的中药提取剂，可起化痰养神、补肾安心之功效，临床多用于神经系统疾病的治疗，但关于其作用机制尚不完全明确[6,7]。本研究旨在观察加兰他敏联合复方海蛇胶囊治疗阿尔茨海默病早发型痴呆的临床效果及对血清肿瘤坏死因子 -α(TNF-α)、白细胞介素 -6、8(IL-6、IL-8)水平的影响。

1 资料与方法

1.1 一般资料

选择我院 2014 年 9 月 ~2016 年 9 月收治的 96 例阿尔茨海默病早发型痴呆患者，符合阿尔茨海默病早发型痴呆相关诊断标准[8]：经认知量表与临床检查明确伴痴呆，两个或者以上的认知功能可见缺损，并呈进行性的恶化，未见意识障碍，年龄在 49~68 岁，并经影像学、血液学等检查排除其他因素所致的认知功能及记忆损伤；与痰浊兼心肾不交证相符[9](智力下降、表情呆滞或者自语、哭笑无常，失眠心悸，且舌红、苔腻、脉细数)；近期无抗精神病药物使用史。排除躯体伴严重疾病；过敏体质；酒精及药物依赖史；精神病史。按治疗方式分组，对照组 23 例男，25 例女；年龄 49~68 岁，平均(62.76± 1.98)岁；实验组 26 例男，22 例女；年龄 50~68 岁，平均(63.08± 1.91)岁。两组一般临床资料的比较差异均无统计学意义(P>0.05)，有比较性。

1.2 治疗方法

对照组予以加兰他敏治疗，起始早晚各口服 2 mg 加兰他敏(江西国药有限责任公司，8 mg/ 片，140823)，待患者未见明显不良反应后逐渐增加计量至每日 12 mg，早晚各 1 次。实验组基于对照组联合复方海蛇胶囊治疗，口服 0.9 g 复方海蛇胶囊(大连泛美制药有限公司，0.3 g/ 粒，140821)，早中晚各 1 次，两组均持续治疗 3 个月，期间均予以相同心理治疗，并禁止使用其他促智药及胆碱酯酶药，对患者不良反应进行记录。

1.3 观察指标

1.3.1 临床疗效观察 患者临床表现全部消失，简易智力状态评分(MMSE)较治疗前增加 5 分以上，且可自如回答问题，并自理生活即显效；临床表现部分消失，MMSE 增加在 2~4 分，可简单回答问题，同时生活大致可自理即好转；临床表现未见缓解或者加剧，MMSE 增加在 1 分一下，生活难以自理即无效。显效及好转均为有效[10]。

1.3.2 血清指标检测 于治疗前及治疗结束时抽取患者 2 mL 空腹静脉血，常规分离血清并保存待检。IL-6、IL-8、TNF-α 予以电化学发光法进行，游离三碘甲状腺原氨酸(FT_3)、游离甲状腺素(FT_4)予以放射免疫法进行。

1.3.3 MMSE 及老年痴呆患者生活质量量表 (QOL-AD) 观察 MMSE 包含视空间、语言、即刻记忆力、延迟记忆、地点定向力、时间定向力、计算力及注意力 7 个方面，总分 30 分，分数与患者智能及记忆状态呈正比。QOL-AD 包含 4 项领域，13 条目，总分为 13~52 分，分数越高表示患者生活质量越好[11,12]。

1.4 统计学分析

数据统计选用 SPPS18.0 进行，计量资料用($\bar{x}\pm s$)表示，组间比较用 t 检验，计数资料用[(例)%]表示，用 x^2 检验比较，以 *P<0.05* 为差异有统计学意义。

2 结果

2.1 两组临床疗效的比较

实验组有效率(93.75%)高于对照组(77.08%)，差异具有统计学意义(*P<0.05*)，见表 1。

表 1 两组临床疗效的比较[例(%)]

Table 1 Comparison the clinical curative effect between two groups[n(%)]

Groups	n	Effective	Improve	Invalid	Efficiency rate
Control group	48	17(35.42)	20(41.67)	11(22.91)	37(77.08)
Experimental group	48	27(56.25)	18(37.50)	3(6.25)	45(93.75)#

Note: Compared with control group, #*P<0.05*.

2.2 两组治疗前后血清 IL-6、IL-8、TNF-α 水平的比较

治疗前，两组血清 IL-6、IL-8、TNF-α 水平比较差异无统计学意义(*P>0.05*)；治疗后，两组血清 IL-6、IL-8、TNF-α 水平均较治疗前降低，且实验组血清 IL-6、IL-8、TNF-α 水平均明显低于对照组(*P<0.05*)，见表 2。

2.3 两组治疗前后血清甲状腺激素水平的比较

治疗前，两组血清甲状腺激素比较差异无统计学意义(*P>0.05*)；治疗后，两组血清 FT_3、FT_4 水平均较治疗前显著上升，且实验组血清 FT_3、FT_4 水平显著高于对照组，差异具有统计学意义(*P<0.05*)，见表 3。

2.4 两组治疗前后 MMSE 及 QOL-AD 的比较

治疗前，两组 MMSE 及 QOL-AD 比较差异无统计学意义(*P>0.05*)；治疗后，两组 MMSE 及 QOL-AD 均较治疗前上升，实验组 MMSE 及 QOL-AD 显著高于对照组(*P<0.05*)，见表 4。

2.5 两组不良反应发生情况的比较

用药期间，对照组 2 例发生恶心、1 例发生口干、1 例发生嗜睡、2 例发生失眠，实验组 2 例发生便秘、2 例发生口干、1 例发生恶心，两组不良反应的发生率比较差异无统计学意义(*P>0.05*)。

表 2 两组治疗前后血清 IL-6、IL-8、TNF-α 水平的比较($\bar{x}\pm s$)

Table 2 Comparison of the serum IL-6, IL-8, TNF-α levels between two groups before and after the treatment ($\bar{x}\pm s$)

Groups	n	Time	IL-6(ng/L)	IL-8(μg/L)	TNF-α(ng/L)
Control group	48	Before treatment	252.61± 31.21	68.22± 8.51	215.87± 26.98
		After treatment	134.26± 16.78'	46.54± 5.80'	189.03± 23.66'
Experimental group	48	Before treatment	253.90± 31.90	66.41± 8.05	213.76± 26.31
		After treatment	87.45± 10.89#'	38.34± 4.77#'	164.88± 20.57#'

Note: Compared with control group, #*P<0.05*; Compared with before treatment, ' *P<0.05*.

表 3 两组治疗前后血清甲状腺激素水平的比较($\bar{x}\pm s$)

Table 3 Comparison of the serum thyroid hormones levels between two groups before and after the treatment ($\bar{x}\pm s$)

Groups	n	Time	FT3(pmol/L)	FT4(pmol/L)
Control group	48	Before treatment	4.46± 0.53	13.63± 1.65
		After treatment	7.03± 0.89'	16.38± 2.02'
Experimental group	48	Before treatment	4.40± 0.67	13.01± 1.78
		After treatment	8.12± 1.07#'	20.56± 2.54#'

表 4 两组治疗前后 MMSE 及 QOL-AD 的比较($\bar{x}\pm s$)

Table 4 Comparison of the MMSE and QOL-AD between two groups before and after the treatment ($\bar{x}\pm s$)

Groups	n	Time	MMSE(分)	QOL-AD(分)
Control group	48	Before treatment	16.05± 2.01	23.07± 2.79
		After treatment	22.58± 2.80'	27.20± 3.42'
Experimental group	48	Before treatment	16.46± 2.34	22.63± 2.81
		After treatment	25.39± 3.11#'	31.45± 3.08#'

Note: Compared with control group, #*P<0.05*; Compared with before treatment, ' *P<0.05*.

3 讨论

阿尔茨海默病早发型痴呆多见于中老年人群,发病时能够导致胆碱能的神经元减少,降低乙酰胆碱的生成与释放,从而造成识别及记忆等系列功能障碍[13]。因此,胆碱酶抑制剂是其首选药物,加兰他敏是乙酰胆碱酶的第 2 代抑制剂,能够于突触后胆碱能不足区域发挥最大的药物活性,对神经元的生存与功能可起到促进作用,避免神经细胞的凋零,其毒性较低,药效持久[14,15]。但有研究显示阿尔茨海默病早发型痴呆单用加兰他敏治疗的效果并不理想[16]。

阿尔茨海默病早发型痴呆属中医学“健忘、痴呆”等范畴,脑部是其主要病位,同时肾、心功能失调可引淤血、痰浊,使脑窍蒙蔽,脑络痹阻,治疗应以化痰养神、补肾安心法[17]。复方海肾胶囊中海蛇性寒、味苦,入脾、肺经,可滋阴壮阳、祛风通络;海参性温,味甘、咸,可养血化燥、补肾益精;石菖蒲性味温、辛,入心、胃经,可益智醒神、开窍化痰、祛湿健胃;远志味苦、性温,入肾、心经,可化痰祛湿、安神益智[18]。现代药理报道海蛇能够利于多巴胺的释放,确保乙酰胆碱与神经递质的平衡;海参能够益智、健脑,提高机体免疫力;石菖蒲能够抗惊厥、镇静;远志能够增强智力及体力,保护脑组织,抗痴呆[19]。本研究结果显示:复方海蛇胶囊治疗者有效率显著高于单用加兰他敏者,提示二者联合治疗能够促进疗效的提高,改善患者的临床症状。

相关研究表明阿尔茨海默病早发型痴呆的病理损伤期间有系列炎症因子参与,IL-6 是机体典型的促炎性因子,由胶质细胞合成并分泌,能够诱导神经元出现凋亡,且可促进 C 反应蛋白、补体等急性蛋白表达,导致发病[20]。IL-8 是多源性的炎性细胞因子,对 T 淋巴细胞、噬碱性粒细胞及中性粒细胞的趋化作用比较强,能够造成炎性细胞集聚,并产生大量活性物,其表达过度时能够导致组织出现不同程度的损伤[21]。TNF-α 能够诱导星形胶质细胞的生存,促进谷氨酸、一氧化氮等神经物质的生成,从而对神经元形成毒性作用[22]。本研究结果显示:联合复方海蛇胶囊治疗后血清 IL-6、IL-8 及 TNF-α 水平均显著低于单用加兰他敏者,说明二者联合治疗能够利于缓解机体的炎症反应,避免其对神经细胞造成的损伤。同时,研究显示阿尔茨海默病早发型痴呆患者血清 FT3、FT4 浓度均较低,说明中枢神经系统功能与甲状腺激素有着紧密联系,且可影响患者的智能状态[23,24]。本研究结果显示:联合复方海蛇胶囊治疗后血清 FT_3、FT_4、MMSE 及 QOL-AD 均显著上升,进一步证实二者联合治疗能够促进患者中社神经系统的改善,提高智力水平。此外,两组用药期间均未见明显不良反应,说明二种治疗方法的安全性相当。

综上所述,加兰他敏联合复方海蛇胶囊治疗阿尔茨海默病早发型痴呆的临床效果优于加兰他敏单药治疗,其能够降低患者血清 IL-6、IL-8 及 TNF-α 浓度,并能提高血清甲状腺激素的水平。

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