

DOI: 10.13241/j.cnki.pmb.2014.01.031

评价抗 SSA、抗 SSB 和抗 α - 胞衬蛋白抗体在诊断干燥综合征中的价值

吴云娟¹ 严孝岭² 张晓军¹ 吕成银¹ 张缪佳^{1△}

(1 南京医科大学第一附属医院 江苏 南京 210029; 2 南京军区南京总医院 江苏 南京 210002)

摘要 目的:评价 SSA、SSB 和胞衬蛋白在诊断干燥综合征(SS)中的价值。**方法:**用酶联免疫吸附试验(ELISA)检测 47 例确诊为 SS 患者、20 例其它自身免疫病(类风湿关节炎 7 例、SLE6 例、自身免疫性肌炎 7 例)和 20 例体检健康者血清抗 SSA、SSB 和 α - 胞衬蛋白抗体,分析三种自身抗体阳性率。**结果:**抗 SSA 抗体、抗 SSB 抗体和抗 α - 胞衬蛋白抗体敏感性分别为 76.6%、38.3%、42.6%;特异性分别为 72.5%、95.0%、82.5%;三种抗体联合检测后敏感性为 89.4%,特异性 50.0%。**结论:**抗 α - 胞衬蛋白抗体与抗 SSA、SSB 抗体联合检测时可提高阳性率,对症状不典型的 SS 患者诊断有一定的补充意义。

关键词:SS; 抗 α - 胞衬蛋白抗体; 抗 SSA 抗体; 抗 SSB 抗体

中图分类号:R442.8, R446 **文献标识码:**A **文章编号:**1673-6273(2014)01-130-02

Diagnostic Value of Anti-SSA, Anti-SSB and Anti-alpha-fodrin Antibody in Sjogren's Syndrome

WU Yun-juan¹, YAN Xiao-ling², ZHANG Xiao-jun¹, LV Cheng-yin¹, ZHANG Miao-jia^{1△}

(1 The First Affiliated Hospital With Nanjing Medical University, Nanjing, Jiangsu, 210029, China;

2 Nanjing General Hospital of Nanjing Command, Nanjing, Jiangsu, 210002, China)

ABSTRACT Objective: To assess the diagnostic value of anti-SSA, anti-SSB and anti-alpha-fodrin antibody in Sjogren's Syndrome (SS). **Methods:** Serum samples were collected from 47 patients with SS, 20 patients with other autoimmune diseases (including 7 cases of rheumatoid arthritis, 13 cases of systemic lupus erythematosus) and 20 normal human controls. Enzyme-linked immunosorbent assay (ELISA) and immunoblotting were performed to test anti-SSA, anti-SSB and anti-alpha-fodrin antibody in these serum samples. **Results:** The sensitivities of anti-SSA, anti-SSB and anti-alpha-fodrin antibody in SS were 76.6%, 38.3% and 42.6%, respectively, and the specificities were 72.5%, 95.0% and 82.5%, respectively. The combination of anti-SSA, anti-SSB and anti-alpha-fodrin antibody had a higher sensitivity (89.4%), but it had a lower sensitivity (50.0%). **Conclusions:** The combination of anti-SSA, anti-SSB and anti-alpha-fodrin antibody can significantly improve the sensitivity to diagnose SS and offer clinical benefits for diagnosis of SS whose symptoms are not typical.

Key words: Anti-SSB; Anti-alpha-fodrin; Anti-SSA; Anti-SSB

Chinese Library Classification (CLC): R442.8, R446 **Document code:** A

Article ID: 1673-6273(2014)01-130-02

干燥综合征(SS)是一种以口、眼干燥为主要表现,累及全身各个系统器官的慢性全身自身免疫性疾病,发病机制尚不明确^[1],腺上皮细胞的功能减退在发病机制中起着关键作用^[2]。目前 SS 的诊断仍依靠唇腺活检及腮腺造影等有创检查,患者依从性差,不利于早期诊断^[3]。SS 患者血清中存在多种抗体,最常见的 Ro/SSA 抗体系统(Ro60 和 Ro52),除了在干燥综合征中出现外,也常出现在系统性红斑狼疮、自身免疫性肌炎等其它自身免疫性疾病中^[4]。抗 SSB 抗体的特异性要高于抗 SSA 抗体,但阳性率只有 40%-50%^[5]。国内外研究发现, α - 胞衬蛋白(α -Fodrin)与 SS 密切相关,在 α -Fodrin 蛋白序列中, α -Fodrin 1~59 位氨基酸序列具有抗原性^[6],近年来发现,该抗体常出现

于经治疗的患者血清中,有一定的早期诊断价值^[7],为此,本研究用 α - 胞衬蛋白、抗 SSA 和抗 SSB 抗体联合检测 47 例干燥综合征、20 例其它自身免疫性疾病患者及 20 例体检健康者血清,探讨其在 SS 中诊断的价值。

1 资料与方法

1.1 标本来源

选择 2012 年 1 月至 2012 年 12 月江苏省人民医院住院及门诊的 SS 患者 47 例,均为女性,年龄(47.6 $\pm$ 13.1)岁(21.0~68.0 岁),均符合 2003 年国家关于 SS 的诊断标准^[8]。同期其它结缔组织病患者 20 例,包括 RA 7 例, SLE 13 例,均符合其国际诊断标准,其中女 18 例,男 2 例,年龄(36.9 $\pm$ 13.4)岁(17.0~57.0 岁);健康体检者 20 例,女 17 例,男 3 例,年龄(40.4 $\pm$ 15.8)岁(19.0~71.0 岁)。

1.2 试剂与方法

SSA、SSB 抗体免疫印迹法检测试剂盒购自德国欧蒙公司, α - 胞衬蛋白 IgA 抗体 ELISA 检测试剂盒由德国 Aesku 诊

作者简介:吴云娟(1985-),女,检验技师,学士,主要研究方向:风湿免疫学 E-mail:wu_yun_juan@163.com

△通讯作者:张缪佳(1961-),女,主任医师,硕士,主要研究方向:风湿免疫学, E-mail:miaojiazhang01@gmail.com

(收稿日期:2013-05-30 接受日期:2013-06-23)

断试剂公司提供;酶联仪为 Bio-Rad-680 型(美国)。

阳性率采用 X^2 检验, $P < 0.05$ 说明有统计学意义。

1.3 统计学分析

分析用 SPSS 13.0 软件进行。SSA、SSB、 α - 胞衬蛋白抗体

2 结果

表 1 三项自身抗体检测结果 阳性率%

Table 1 Results of three kinds of autoantibodies Positive rate%

Group	N	Anti-SSA antibody	Anti-SSB antibody	Anti- α -Fodrin	Combined detection
SS	47	76.6(36/47)*	38.3(18/47)*	42.6(20/47)*	89.4(42/47)*
Disease Control	20	55.0(11/20)	10.0(2/20)	20.0(4/20)	70.0(14/20)
Normal Control	20	0.0(0/20)	0.0(0/20)	15.0(3/20)	15.0(3/20)
Total Control	40	27.5(11/40)	5.0(2/40)	17.5(7/40)	50.0(20/40)

注:SS 组与对照总计比较,* $P < 0.05$ 。

Note:compare SS group with total control group.* $P < 0.05$.

3 种自身抗体阳性率均显著高于其他结缔组织病和健康体检者(均 $P < 0.05$)。抗 SSA 抗体、抗 SSB 抗体和抗 α - 胞衬蛋白抗体敏感性分别为 76.6%、38.3%、42.6%,见表 1;特异性分别为 72.5%、95.0%、82.5%;三种抗体联合检测后敏感性为 89.4%,特异性 50.0%。

3 讨论

SS 是一种慢性自身免疫性疾病,主要以淋巴细胞浸润泪腺、唾液腺引起眼干、口干为特征,这种浸润有时发生在腺外组织,如肺、肾、肝脏,与恶性肿瘤也有一定的相关性,特别是非霍奇金淋巴瘤^[9,10]。大多数浸润细胞为 CD4⁺T 细胞,发病率约为 0.5%。在美国,因为 SS 每年需支出 100 多亿美元,仅低于类风湿性关节炎^[11]。尽管 SS 的发病率较高,但是由于临床症状不典型,而且缺乏敏感性高,特异性强的诊断方法,所以 SS 的早期诊断至今都是一个难题。

近期,抗 α - 胞衬蛋白抗体作为 SS 诊断的一个补充性标志物引起了人们的热议。 α - 胞衬蛋白是一个在细胞内广泛表达的 240-KDa 的蛋白质,与 β - 胞衬蛋白共同组成一个同质二聚体。在慢性病毒感染引起细胞凋亡时, α - 胞衬蛋白被细胞凋亡蛋白酶 3 裂解成 150 和 120KDa 的片段。这两个片段都曾在大量 SS 病人的唾液腺中检测到过^[12]。机体免疫系统对这些片段不耐受,就会产生相应的抗体^[13]。He J 等报道抗 α - 胞衬蛋白抗体 IgG 在 SS 病人中的敏感性为 77.3%,特异性为 90%^[14]。在近期的研究中,用 α - 胞衬蛋白裂解的大片段作抗原检测,发现抗 α - 胞衬蛋白抗体在美国 SS 病人中的阳性率甚至达到 98%^[15]。但是国内的大部分报道都认为抗 α - 胞衬蛋白抗体在中国 SS 病人中的阳性率较低,如任义乐等^[16]报道抗 α - 胞衬蛋白 IgA 抗体在 pSS 病人中的阳性率为 33.3%。本文的研究与国内的报道较一致,抗 α - 胞衬蛋白抗体在 SS 病人中的阳性率为 42.6%。经分析可能为国内使用的检测方法、试剂与国外差别较大,而且人种也有差别。此外,有文献报道在 SS 患者的泪液和唾液中也存在抗 α - 胞衬蛋白抗体,阳性率 20%-44%^[17,18],联合检测血清、泪液及唾液中的抗 α - 胞衬蛋白抗体,可以明显提高检出率^[7,19]。

抗 SSA、SSB 抗体是用来辅助诊断 SS 的经典生物标志物。但是当医生高度怀疑就诊患者为 SS,而抗 SSA、SSB 抗体又不支持这一诊断时,就必须对病人进行唇腺活检或腮腺造影等创

伤性检查确诊,这对病人的伤害很大。近年来发现外分泌腺细胞膜上蕈碱受体 3(M3)抗体的产生于 SS 的发病密切相关^[19]。此外还发现抗 SSA、SSB 抗体阴性的 SS 患者中存在一些抗体,如抗唾液腺蛋白 -1 抗体(SP-1),抗碳酸酐酶 6 (CA6)抗体和抗腮腺分泌蛋白(PSP)抗体,但阳性率不高^[20]。抗 α - 胞衬蛋白抗体与抗 SSA、SSB 抗体联合检测时可以将敏感性提高到 89.4%,对症状不典型的 SS 患者诊断有一定的补充意义。

参考文献(References)

- [1] 张孝丰,汪一萍,罗建平. I 抗 SSA 抗体、抗 SSB 抗体,抗 α - 胞衬蛋白联合检测在干燥综合征中的诊断价值 [J]. 现代实用医学, 2011, 23(12): 1372-1374
- [2] Zhang Xiao-feng, Wang Yi-ping, Luo Jian-ping. I Diagnostic Value of Anti-SSA, Anti-SSB and Anti-alpha-fodrin Antibody in Sjogren's Syndrome[J]. Mordern Practical Medicine, 2011, 23(12): 1372-1374
- [3] Venables PJ. Sjogren's Syndrome [J]. Best Pract Res Clin Rheumatol, 2004, 18(3): 313-329
- [4] Haneji N, Nakamura T, Takio K, et al. Identification of alpha-fodrin as a candidate autoantigen in primary Sjogren's Syndrome [J]. Science, 1997, 276(5312): 604-607
- [5] Zou Qiong, Jiao Ju, Zou Min-hong, et al. Semi-quantitative evaluation of salivary gland function in Sj gren's syndrome using salivary gland scintigraphy[J]. Clin. Rheumatol, 2012, 31(12): 1699-1705
- [6] Caterina Defendenti, Fabiola Atzeni, maria Francesca, et al. Clinical and laboratory aspects of Ro/SSA-52 autoantibodies[J]. Autoimmunity Review, 2011, 10: 150-154
- [7] Vitali C, Bombardieri S, Mout80poulo s HM, et al. Preliminary criteria for the chssificatbn of sjogren's Byndrome. Resoultts of a prospective concened action supponed by the European Community [J]. Arthritis Rheum, 1993, 36: 340
- [8] Witte T. Diagnostic markers of Sjogren's syndrome[J]. Dev Ophthalmol, 2010, 45: 123-128
- [9] 中华医学会风湿病学分会.干燥综合征诊治指南(草案)[J]. 中华风湿病学杂志, 2003, (7): 446
- [10] Chinese Medical Association. Sjogren's syndrome diagnosis and treatment guidelines (draft)[J]. Chinese Journal of Rheumatology, 2003, (7): 446
- [11] Fleming Cole N, Toy EC, Baker B. Sjogren's Syndrome [J]. Prim Care Update Ob Gyns, 2001, 8(1): 48-51

(下转第 113 页)

- of a novel endogenous peptide ligand for the human APJ receptor[J]. *Biochem Biophys Res Commun*, 1998, 251: 471-476
- [6] Kushner FG, Hand M, Smith SC Jr, et al. 2009 focused ACC / AHA guidelines for the management of patients with ST elevation myocardial infarction ACC / AHA / SCAI guidelines on percutaneous coronary intervention a report of the American College of Cardiology Foundation / American Heart Association Task Force on Practice Guidelines[J]. *J Am Coll Cardiol*, 2009, 54(23): 2205-2241
- [7] Department of noncommunicable disease surveillance. Definition, diagnosis and classification of diabetes mellitus and its complications. Report of a WHO consultation. Part 1. Diagnosis and classification of diabetes mellitus [J]. Geneva: World Health Organisation, 1999, 151: 365-372
- [8] Feng J, Li SS, Hang QS, et al. Involvement of the activation of cathepsin in the inhibition of oxidative stress related cardiac hypertrophy by Apelin[J]. *Regul Pept*, 2012, 133(1-3): 527-530
- [9] Zhong JC, Yu XY, Huang Y, et al. Apelin modulates aortic vascular tone via endothelial nitric oxide synthase phosphorylation pathway in diabetic mice[J]. *Cardiovasc Res*, 2007, 74: 388-395
- [10] Chandra S, Razavi H, Agrawal R, et al. Apelin Deficient Mice Demonstrate Worsening Pulmonary Hypertension in a Nitric Oxide Dependent Manner[J]. *Circulation*, 2009, 120: 128-134
- [11] Jia YX, Pan CS, Zhang J, et al. Apelin protects myocardial injury induced by isoproterenol in rats[J]. *Regul Pept*, 2006, 133(1-3): 147-154
- [12] Zhang M, Yang PL, Tong J, et al. Role of apelin in rat myocardial ischemic preconditioning and ischemia reperfusion injury[J]. *Chinese Journal of Pathophysiology*, 2007, 23(11): 2112-2118
- [13] Gobe G, Willgoss D, Hogg N. Cell survival or death in renal epithelium after ischemia / reperfusion injury [J]. *Kidney Int*, 1999, 56(4): 1299-1304
- [14] Tao J, Zhu W, Li Y, et al. Apelin-13 protects the heart against ischemia-reperfusion injury through inhibition of ER-dependent apoptotic pathways in a time-dependent fashion [J]. *Peptides*, 2011, 30(4): 1471-1486
- [15] Zeng XJ, Zhang LK, Wang HX, et al. Apelin protects heart against ischemia/reperfusion injury in rat[J]. *Peptides*, 2009, 30(6): 1144-1152
- [16] Hashimoto T, Kihara M, Ishida J, et al. Apelin stimulates myosin light chain phosphorylation in vascular smooth muscle cells [J]. *Arterioscler Thromb Vasc Biol*, 2006, 26: 1267-1272
- [17] Yu Y, Huang DJ. Effects of exogenous Apelin on cardiomyocyte hypertrophy[J]. *Chin Heart*, 2006, 18(2): 185-189
- [18] Henley DE, Buchanan F, Gibson R, Douthwaite JA, Wood SA, Woltersdorf WW, Catterall JR, Lightman SL. Plasma Apelin levels in obstructive sleep apnea and the effect of continuous positive airway pressure therapy[J]. *J Endocrinol*, 2009, 203: 181-188
- [19] Bonetti PO, Iermano LO, Iermano A, et al. Endothelial dysfunction, a marker of atherosclerotic risk [J]. *Arterioscler Thromb Vasc Biol*, 2003, 23: 168-175
- [20] Navarro S, Ricart JM, Medina P, et al. Activated protein C levels in Behcet's disease and risk of venous thrombosis [J]. *Br J Haematol*. 2004, 126(4): 550-557
- [21] Higuchi K, Magnusson C, Ahren B, et al. The apelin receptor is expressed in pancreatic islets and its ligand, Apelin inhibits insulin secretion in mice[J]. *Regul Pept*, 2005, 131(3): 122-127

(上接第 131 页)

- [10] Shoenfeld Y, Selmi C, Zimlichman E, et al. The autoimmunologist: geoepidemiology, a new center of gravity and prime time for autoimmunity[J]. *Autoimmun*, 2008, 31: 325-330
- [11] Martin SJ, O'Brien GA, Nishioka WK, et al. Proteolysis of fodrin (non-erythroid spectrin) during apoptosis[J]. *The Journal of Biological Chemistry*, 1995, 270(12): 6425-6428
- [12] Garcia-Carrasco M, Mendoza-Pinto C, Jimenez-Hernandez C, et al. Serologic features of primary Sjogren's syndrome: clinical and prognostic correlation[J]. *Int J Clin Rheumatol*, 2012, 7(6): 651-659
- [13] Torsten Witte. Diagnostic Markers of Sjogren's Syndrome [J]. *Dev Ophthalmol*, 2010, 45: 123-128
- [14] He J, Fang W, Li ZG. The application of combined detection of autoantibodies in primary Sjogren's syndrome[J]. *Chinese Journal of Internal Medicine*, 2008, 47(5): 366-368
- [15] Maruyama T, Saito I, Hayashi Y, et al. Molecular analysis of the human autoantibody response to alpha-fodrin in Sjogren's syndrome reveals novel apoptosis-induced specificity[J]. *Am J Pathol*, 2004, 165(1): 53-61
- [16] 任义乐, 丁翔, 常新, 等. 抗 α -胞衬蛋白抗体在原发性干燥综合征诊断中的意义[J]. *江苏医药*, 2010, 36(11): 1276-1277
- Ren Yi-le, Ding Xiang, Chang Xin, et al. The diagnostic significance of anti- α -Fodrin antibody in primary Sjogren's syndrome[J]. *Jiangsu Medical Journal*, 2010, 36(11): 1276-1277
- [17] Sumida Takayuki, Iizuka Mana, Asashima Hiromitsu, et al. Pathogenic role of anti-M3 muscarinic acetylcholine receptor immune response in Sjogren's syndrome[J]. *Presse Med*, 2012, 41(9): 461-466
- [18] Yavuz Sule, Toker Ebru, Bicakcigi Muge, et al. Comparative analysis of autoantibodies against α -fodrin in serum, tear fluid, and saliva from patients with Sjogren's syndrome[J]. *J. Rheumatol*, 2006, 33(7): 1289-1292
- [19] 许珂, 侯云霞, 张琳, 等. 血清和唾液抗 α -胞衬蛋白抗体检测及其在干燥综合征中的意义[J]. *中华风湿病学杂志*, 2008, 12(6): 386-389
- Xu Ke, Hou Yun-xia, Zhang Lin, et al. Value of serum and saliva anti- α -Fodrin antibodies in patients with Sjogren's syndrome [J]. *Chinese Journal of Rheumatology*, 2008, 12(6): 386-389
- [20] Shen Long, Suresh Lakshmanan, Lindemann Matthew, et al. Novel autoantibodies in Sjogren's syndrome[J]. *Clin Immunol*, 2012, 145(3): 251-255