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氯沙坦钾治疗特发性膜性肾病对血清抗 PLA2R 抗体的影响 *

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摘要 目的:探讨氯沙坦钾治疗特发性膜性肾病对血清抗磷脂酶 A2 受体(Phospho lipase A2 receptor,PLA2R)抗体的影响。**方法:**2014 年 8 月到 2018 年 8 月选择在西安交通大学医学院附属汉中 3201 医院(本院)肾内科诊治的特发性膜性肾病患者 78 例,根据随机数字表法分为两组,各 39 例,对照组给予常规腹膜透析治疗,观察组在对照组治疗的基础上给予氯沙坦钾治疗,两组都治疗观察 3 个月,记录血清抗 PLA2R 抗体表达变化。**结果:**观察组治疗的总有效率为 100.0 %,显著高于对照组的 87.2 % (P<0.05)。两组治疗后的血尿素氮(Blood urea nitrogen, BUN)、肌酐(Creatine, CREA)、尿酸(Uric acid, UA)值都低于治疗前,且观察组也显著低于对照组 (P<0.05)。两组治疗后的血清超氧化物歧化酶 (Superoxide Dismutase, SOD)、谷胱甘肽过氧化酶 (Glutathione Peroxidase, GSH-Px)值都高于治疗前,丙二醛(Malonic dialodehyde, MDA)值低于治疗前,且观察组变化更加显著(P<0.05)。两组治疗后的血清抗 PLA2R 抗体表达水平显著低于治疗前(P<0.05),观察组也显著低于对照组(P<0.05)。**结论:**氯沙坦钾治疗特发性膜性肾病能抑制血清抗 PLA2R 抗体表达,调节氧化应激功能,从而促进肾功能的改善,提高患者的治疗效果。

关键词:氯沙坦钾;特发性膜性肾病;磷脂酶 A2 受体;疗效
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Effects of Losartan Potassium on Serum Anti-PLA2R Antibody in Patients with Idiopathic Membranous Nephropathy*

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ABSTRACT Objective: To investigate the effects of losartan potassium on serum phospholipase A2 receptor (PLA2R) antibody in patients with idiopathic membranous nephropathy. **Methods:** From August 2014 to August 2018, 78 patients with idiopathic membranous nephropathy who were diagnosed and treated in the Department of Nephrology, Hanzhong 3201 Hospital of Xi'an Jiaotong University School of Medicine were equally divided into the observation group and control group accorded to the random number table. The control group was given conventional peritoneum dialysis treatment, and the observation group was treated with losartan potassium on the basis of the control group, and the two groups were treated for 3 months, and the serum anti-PLA2R antibody expression was recorded. **Results:** The total effective rates of the observation group was 100.0%, which was significantly higher than that of the control group (87.2 %)(P<0.05). The BUN, CREA and UA values of the two groups after treatment were lower than those before treatment, and the observation group was also significantly lower than the control group (P<0.05). The levels of serum GSH-PX and SOD values of the two groups after treatment were higher than those before treatment, and the MDA values were lower than before treatment, and the changes in the observation group were more significant (P<0.05). The serum anti-PLA2R antibody expression levels in the two groups after treatment were significantly lower than that before treatment, and the observation group were also significantly lower than the control group (P<0.05). **Conclusion:** Losartan potassium treatment of idiopathic membranous nephropathy can inhibit the expression of anti-PLA2R antibody and regulate oxidative stress, thereby promote the improvement of renal function and improving the therapeutic effect of patients.

Key words: Losartan potassium; Idiopathic membranous nephropathy; Phospholipase A2 receptor; Effect
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前言

特发性膜性肾病(Idiopathic membranous nephropathy,IMN)是一种常见的慢性肾脏病,发病对象以中老年为主,其临床表

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现为肾病综合征或无症状性蛋白尿[1,2]。特发性膜性肾病通常起病隐匿,大约一半左右的患者由于没有接受规范化的治疗最终进展为终末期肾脏病[3]。已有研究认为 IMN 的发病机制为免疫复合物介导的肾脏受损,之后沉积于肾小球,形成膜攻击复合物 (C5b-9)[4,5]。氯沙坦钾是一种血管紧张素Ⅱ受体拮抗剂(Angiotensin Ⅱ receptor blocker, ARB),可通过阻断血管紧张素Ⅱ(AngⅡ)与 ATⅠ受体结合,从而抑制 AngⅡ的致病作用,有效的保护肾脏[6,7]。并且氯沙坦钾也具有保护肾功能、减轻蛋白尿的作用,可阻止足细胞损伤,从而减少糖尿病肾病蛋白尿的排泄[8]。抗磷脂酶 A2 受体(phospho lipase A2 receptor,PLA2R)是存在于人类足细胞表面的膜蛋白,与 IgG4 共定位于 IMN 患者肾小球的免疫沉积物中,PLA2R 是导致 IMN 的主要抗原之一[9,10]。血清 PLA2R 抗体水平对特发性膜性肾病的诊断、预后判断等具有重要临床应用价值[11,12],但是在疗效监测中还无相关报道。本文具体探讨了氯沙坦钾治疗特发性膜性肾病对血清抗 PLA2R 抗体的影响,为应用氯沙坦钾治疗特发性膜性肾病提供了临床资料,现总结报告如下。

1 资料与方法

1.1 研究对象

选择 2014 年 8 月到 2018 年 8 月在本院诊治的特发性膜性肾病患者 78 例,纳入标准:经皮肾穿刺活检后病理证实为特发性膜性肾病;首次入院;患者首诊时 24 h 尿蛋白定量为(3.5-6.0) g;年龄 20-70 岁;医院伦理委员会批准了此次研究。排除标准:乙型肝炎病毒、丙型肝炎病毒感染导致肾功能损害者;合并自身免疫性疾病的患者;遗传性肾病、糖尿病肾病等患者;合并原发恶性肿瘤患者。

根据随机数字表法分为两组,各 39 例,两组的基线资料对比无统计意义(P>0.05),具有可比性。见表 1。

表 1 两组基线资料对比

Table 1 Comparison of general data between the two groups

Groups	n	Age(years)	Clinical stage (Ⅰ/Ⅱ/Ⅲ)	Gender (male / female)	Baric index(kg/m²)	Course(year)
Research group	39	50.24±2.12	20/10/9	22/17	22.48±1.84	3.19±0.22
Control group	39	50.11±1.98	21/9/9	25/14	22.14±2.91	3.28±0.31

1.2 治疗方法

对照组:给予常规腹膜透析治疗,均用百特的双联腹膜透析管路,3-4 次 /d,腹透液 2000 mL/ 次。

观察组:在对照组治疗的基础上给予氯沙坦钾治疗,口服氯沙坦钾(国药准字 H20070264,扬子江药业集团四川海蓉药业)50 mg/ 次,1 次 /d。

两组都治疗观察 3 个月,在治疗过程中给予患者低脂优质蛋白饮食,对症给予降脂、抗凝等基础治疗。

1.3 观察指标

(1)所有患者在治疗前后采集空腹静脉血,使用生化分析仪(日本日立 7600-110 型) 测定 BUN、CREA、UA 含量,UA 检测采用脲酸酶法,BUN、CREA 检测采用酶法。(2)选择上述的血液样本,离心机 3500 r/min 4 ℃高速离心 10 min,分离血清,置于 -70 ℃冰箱待用,采用酶联免疫法检测 GSH-PX、SOD、MDA 含量。(3)疗效标准:临床控制:尿常规检查蛋白转阴性,24 h 尿蛋白定量正常,肾功能正常;显效:尿常规显示尿蛋白减少 2 个"+",或 24 h 尿蛋白定量减少≥ 40 %,肾功能正常或与正常值相差不超过 15 %;无效:实验室检查均无改善或加重者。(临床控制 + 显效)/ 组内例数× 100.0 %= 总有效率。(4)取上述的血清样本,采用酶联免疫法检测血清抗 PLA2R 抗体表达水平,检测试剂盒购自上海源叶生物公司。

1.4 统计方法

选择 SPSS22.00 软件,计量数据用($\bar{x}\pm s$)示,行 t 检验,计数数据用%示,行 χ^2 检验,P<0.05 为有统计学差异。

2 结果

2.1 总有效率对比

观察组治疗的总有效率为 100.0 %,显著高于对照组的 87.2 %(P<0.05)。见表 2。

表 2 两组总有效率对比(例,%)

Table 2 Comparison of total efficiency between the two groups (n, %)

Groups	n	Clinical control	Excellence	No avail	Total effective rate
Research group	39	35	4	0	39(100.0%)*
Control group	39	20	14	5	34(87.2%)

Note: *P<0.05 means comparison with the control group.

2.2 肾功能指标变化对比

两组治疗后的血清 BUN、CREA、UA 值都低于治疗前,且观察组也显著低于对照组(P<0.05)。见表 3。

2.3 氧化应激指标变化对比

两组治疗后的血清 GSH-PX、SOD 值都高于治疗前,MDA 值低于治疗前,且观察组变化更加显著(P<0.05)。见表 4。

2.4 血清抗 PLA2R 抗体表达对比

两组治疗后的血清抗 PLA2R 抗体表达水平显著低于治疗前,且观察组也显著低于对照组(P<0.05)。见表 5。

表 3 两组治疗前后肾功能指标变化对比($\bar{x}\pm s$)

Table 3 Comparison of renal function indicators before and after treatment in both groups ($\bar{x}\pm s$)

Groups	n	BUN(mmol/L)		CREA(mmol/L)		UA(mmol/L)	
		Pretherapy	Post-treatment	Pretherapy	Post-treatment	Pretherapy	Post-treatment
Research group	39	5.27±0.21	4.21±0.45*#	72.22±7.87	44.52±4.11*#	334.98±31.38	223.10±24.02*
Control group	39	5.38±0.38	4.78±0.33*	73.20±7.88	56.29±3.82*	338.87±35.98	287.77±33.01*

Note: *P<0.05 means comparison with Pretherapy, #P<0.05 means simultaneous comparison with the control group of Post-treatment.

表 4 两组治疗前后氧化应激指标变化对比($\bar{x}\pm s$)

Table 4 Comparison of changes in oxidative stress indicators before and after treatment in both groups($\bar{x}\pm s$)

Groups	n	GSH-PX(U/L)		SOD(U/mL)		MDA(μmol/L)	
		Pretherapy	Post-treatment	Pretherapy	Post-treatment	Pretherapy	Post-treatment
Research group	39	167.03±18.30	203.10±18.33*#	75.99±2.44	91.83±4.02*#	17.55±2.11	12.00±3.28*#
Control group	39	168.00±19.22	184.02±17.83*	76.02±3.11	82.99±5.82*	17.89±1.87	15.00±2.12*

Note: *P<0.05 means comparison with Pretherapy, #P<0.05 means simultaneous comparison with the control group of Post-treatment

表 5 两组治疗前后血清抗 PLA2R 抗体表达对比(ng/L,$\bar{x}\pm s$)

Table 5 Comparison of serum anti-PLA2R antibody expression before and after treatment in both groups (ng/L, $\bar{x}\pm s$)

Groups	n	Pretherapy	Post-treatment
Research group	39	834.24±93.33	78.02±5.98*#
Control group	39	821.03±98.91	145.93±6.88*

Note: *P<0.05 means comparison with Pretherapy, #P<0.05 means simultaneous comparison with the control group of Post-treatment.

3 讨论

IMN 是成年人肾小球疾病常见的原因之一,是一种由抗体介导的自身免疫性疾病。其常见病因包括自身免疫性疾病、毒物、感染等[13]。该病具有很强的异质性,是一种难治的疾病,其发病率占全部原发性肾小球疾病的 9.0 %左右[14]。现代研究显示 IMN 的发生发展由多种因素共同作用、调控[15]。该病的治疗应以肾脏病病理学及药理学知识为基础,对患者病情进行全面评估,根据具体案例综合考虑给出最适合的治疗方案[16]。

在 IMN 患者中,肾脏局部的 RAS 被异常激活,在 AngⅡ的持续刺激下,肾小球内压力增加,导致足细胞与基底膜脱离,形成蛋白尿[17]。AngⅡ可通过与 ATⅠ结合,进一步损伤足细胞,使尿蛋白排出,进而导致肾小球的硬化[18]。氯沙坦钾是一种血管紧张素转化酶受体拮抗剂类药物,可通过改善肾小球滤过膜的通透性来减少蛋白尿的排出[19]。本研究显示观察组的治疗总有效率显著高于对照组;两组治疗后的血 BUN、CREA、UA 值都低于治疗前,观察组也显著低于对照组,表明氯沙坦钾的应用能促进改善患者的肾功能,提高患者的治疗效果。

特发性膜性肾病是导致成人肾病综合征的常见病理类型,80 %表现为肾病综合征,部分患者将进展为慢性肾衰竭[20]。氧化应激是机体的抗氧化 / 氧化系统失衡, 对机体产生伤害。IMN 患者中活性氧簇(Reactive oxygen species,ROS)水平过高,使患者氧化应激增强,表现为和抗氧化防御能力减弱与氧化应激的亢奋[21]。本研究显示两组治疗后的血清 GSH-PX、SOD 值都高于治疗前,MDA 值低于治疗前, 且观察组的变化更加显著,表明氯沙坦钾的应用能改善机体的氧化应激水平。从机制上分析,氯沙坦钾可能抑制血管紧张素Ⅱ诱导细胞产生的ROS,通过下调各亚基的表达, 从而抑制还原型辅酶氧化酶的活性,阻断晚期糖基化终末产物的产生,发挥抗炎抗氧化作用[22,23]。

PLA2R 存在足细胞膜上,能与相应蛋白形成免疫复合物,激活补体,导致足细胞病变进而产生蛋白尿[23,24]。PLA2R 也能与配体结合,引起细胞增殖、迁移等[25,26],但是在肾组织的生理作用还不明确。血清抗 PLA2R 抗体阳性的特发性膜性肾病患者较阴性患者更容易发展为大量蛋白尿并且需要接受免疫抑制剂的治疗, 在患者的治疗过程中监测抗 PLA2R 抗体的变化能够提前预判药物对特发性膜性肾病患者的治疗效果[27]。当前也有研究显示 PLA2R 与抗 PLA2R 抗体形成的免疫复合物积聚在肾小球基底膜上,使得血清 BUN、CREA、UA 水平升高,也可以作为肾功能的判断指标,也可判断患者的病情[28-30]。本研究显示两组治疗后的血清抗 PLA2R 抗体表达水平显著低于治疗前, 观察组也显著低于对照组, 表明氯沙坦钾的应用能抑制 PLA2R 的表达。

总之, 氯沙坦钾治疗特发性膜性肾病能抑制血清抗 PLA2R 抗体表达, 调节氧化应激功能, 从而促进肾功能的改善,提高患者的治疗效果。

参 考 文 献(References)

[1] Cheng G, Liu J, Gilbert A, et al. Serum phospholipase A2 receptor antibodies and immunoglobulin G subtypes in adult idiopathic membranous nephropathy: Clinical value assessment [J]. Clin Chim Acta, 2019, 490(2): 135-141

[2] Chi JN, Lai TS, Wu CF, et al. The relationship of anti-phospholipase

A2 receptor antibody and C5a complement with disease activity and short-term outcome in idiopathic membranous nephropathy [J]. J Formos Med Assoc, 2019, 118(5): 898-906

[3] Diaz M, Agraz I, Soler MJ. Anti-phospholipase A2 receptor antibody and spontaneous remission in membranous nephropathy [J]. Clin Kidney J, 2019, 12(1): 33-35

[4] Garcia-Vives E, Sole C, Moline T, et al. Antibodies to M-type phospholipase A2 receptor (PLA2R) in membranous lupus nephritis [J]. Lupus, 2019, 28(3): 396-405

[5] Han WW, Tang LJ, Kong XL, et al. Clinical significance of autoantibodies in the assessment and treatment of idiopathic membranous nephropathy[J]. Exp Ther Med, 2019, 17(3): 1825-1830

[6] Fu XJ, Hu SY. Shenduning Granule Attenuates Renal Injury from Oxidative Stress through the Nuclear Factor Erythroid 2-Related Factor 2/Antioxidant Response Element Pathway [J]. Pharmacology, 2019, 103(5-6): 236-245

[7] Kang JS, Lee SJ, Lee JH, et al. Angiotensin II-mediated MYH9 downregulation causes structural and functional podocyte injury in diabetic kidney disease[J]. Sci Rep, 2019, 9(1): 7679-7682

[8] Koszegi S, Molnar A, Lenart L, et al. RAAS inhibitors directly reduce diabetes-induced renal fibrosis via growth factor inhibition [J]. J Physiol, 2019, 597(1): 193-209

[9] Kamyshova ES, Bobkova IN, Gorelova IA, et al. Genetic determinants of the development and course of membranous nephropathy [J]. Ter Arkh, 2018, 90(6): 105-111

[10] Kaur G, Chen G. Membranous or membranous-like GN: A case report of massive proteinuria, positive serum with negative PLA2R on biopsy[J]. Clin Case Rep, 2018, 6(11): 2198-2201

[11] Keri KC, Blumenthal S, Kulkarni V, et al. Primary membranous nephropathy: comprehensive review and historical perspective [J]. Postgrad Med J, 2019, 95(1119): 23-31

[12] Khorsan R, Hanna RM, Ameen K, et al. Primary membranous nephropathy with concomitant IgA nephropathy [J]. Saudi J Kidney Dis Transpl, 2019, 30(2): 531-536

[13] Zhang D, Wu Y, Zhang C, et al. Compared staining of the phospholipase A2 receptor in the glomeruli of Chinese adults and children with idiopathic membranous nephropathy [J]. Pathol Res Pract, 2019, 215(5): 952-956

[14] Yao Y, Li Y, Zeng X, et al. Losartan Alleviates Renal Fibrosis and Inhibits Endothelial-to-Mesenchymal Transition (EMT) Under High-Fat Diet-Induced Hyperglycemia [J]. Front Pharmacol, 2018, 29(9): 1213-1224

[15] Zhao J, Chan YC, He B, et al. A patent herbal drug Yi-Shen-Hua-Shi granule ameliorates C-BSA-induced chronic glomerulonephritis and inhabits TGFbeta signaling in rats [J]. J Ethnopharmacol, 2019, 236: 258-262

[16] Zhao J, Cheng Q, Liu Y, et al. Atorvastatin alleviates early hypertensive renal damage in spontaneously hypertensive rats [J]. Biomed Pharmacother, 2019, 109: 602-609

[17] Hara S, Tsuji T, Fukasawa Y, et al. Clinicopathological characteristics of thrombospondin type 1 domain-containing 7A-associated membranous nephropathy[J]. Virchows Arch, 2019, 474(6): 735-743

[18] Huang B, Zhang Y, Wang L, et al. Phospholipase A2 Receptor Antibody IgG4 Subclass Improves Sensitivity and Specificity in the Diagnosis of Idiopathic Membranous Nephropathy [J]. Kidney Blood Press Res, 2019, 2(12): 1-10

[19] Kuczborska K, Gozdowska J, Chmura A, et al. Successful Pediatric Kidney Transplantation Into an Adult Recipient: A Case Report [J]. Transplant Proc, 2018, 50(10): 3920-3922

[20] Saulnier PJ, Darshi M, Wheelock KM, et al. Urine metabolites are associated with glomerular lesions in type 2 diabetes[J]. Metabolomics, 2018, 14(6): 84-93

[21] Sen Z, Weida W, Li Y, et al. Nicousamide attenuates renal dysfunction and glomerular injury in remnant kidneys by inhibiting TGF-beta1 internalisation and renin activity [J]. Eur J Pharmacol, 2019, 845: 74-84

[22] Liu Y, Li L, Qiu M, et al. Renal and cerebral RAS interaction contributes to diabetic kidney disease [J]. Am J Transl Res, 2019, 11 (5): 2925-2939

[23] Latt KZ, Honda K, Thiri M, et al. Identification of a two-SNP PLA2R1 Haplotype and HLA-DRB1 Alleles as Primary Risk Associations in Idiopathic Membranous Nephropathy [J]. Sci Rep, 2018, 8(1): e15576

[24] Li C, Li H, Wen YB, et al. Analysis of predictive factors for immunosuppressive response in anti-phospholipase A2 receptor antibody positive membranous nephropathy [J]. BMC Nephrol, 2018, 19(1): 354-361

[25] Lu H, Cui Z, Zhou X J, et al. Plasma exchange and rituximab treatments in primary membranous nephropathy combined with crescentic glomerulonephritis: A case report[J]. Medicine (Baltimore), 2019, 98(18): e15303

[26] Mohammad Ibrahim WH, Aly MG, Abdo MK, et al. Primary Membranous Glomerulonephritis-associated with Schistosomal Nephropathy[J]. Indian J Nephrol, 2019, 29(2): 140-142

[27] Muhsin SA, Masia R, Smith RN, et al. Phospholipase A2 receptor-associated membranous nephropathy in a patient with IgG4-related disease: A case report[J]. Medicine (Baltimore), 2019, 98(20): e15616

[28] Provatopoulou S, Kalavrizioti D, Stangou M, et al. Circulating anti-phospholipase A2 receptor antibodies as a diagnostic and prognostic marker in Greek patients with idiopathic membranous nephropathy - a retrospective cohort study[J]. Rom J Intern Med, 2019, 57(2): 141-150

[29] Qin AB, Su T, Wang SX, et al. Mercury-associated glomerulonephritis: a retrospective study of 35 cases in a single Chinese center[J]. BMC Nephrol, 2019, 20(1): 228-238

[30] Rovin BH, Almaani S, Malvar A. Reimagining the kidney biopsy in the era of diagnostic biomarkers of glomerular disease[J]. Kidney Int, 2019, 95(2): 265-267