

基于中西医病证特点的慢性肾小球肾炎动物模型的临床吻合度分析

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[摘要] 慢性肾小球肾炎(CGN)是临床常见的自身免疫反应的慢性肾小球疾病,其发病机制复杂,且尚未被完全阐明。现代医学没有特异的治疗方法。建立符合中西医病证特点的CGN动物模型将有助于揭示CGN发病机制、药物评级及完善治疗方案。该文基于CGN临床诊断标准建立CGN中西医辨证标准,通过对CGN动物模型文献总结及分析归纳,发现CGN模型以大鼠为主建模,方法多为单因素诱导和双因素诱导,主要表现疾病特征是肾炎相关的症状。其中,单因素与双因素诱导CGN大鼠模型多具备较高的西医临床吻合度,但中医临床吻合度不足。此外,CGN中医证候模型以脾肾气虚证与肺肾气虚证为主,脾肾阳虚证、肝肾阴虚证和气阴两虚证模型稍不足。因此,制备新型及完善CGN动物模型,为CGN的中西医病证机制探索及治疗研究提供符合临床前模型。

[关键词] 慢性肾小球肾炎; 临床吻合度; 中西医病证特征; 动物模型

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Fitting Degrees of Animal Models of Chronic Glomerulonephritis with Clinical Characteristics in Western Medicine and Traditional Chinese Medicine

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[Abstract] Chronic glomerulonephritis (CGN) is a common clinical chronic glomerular disease caused by autoimmune reaction, the pathogenesis of which is complex and has not been fully elucidated. There is no specific treatment method in modern medicine. The establishment of an animal model of CGN in accordance with its characteristics in western medicine and traditional Chinese medicine will help to reveal the pathogenesis of CGN, rate drugs, and improve the treatment plan. Based on the clinical diagnostic criteria of CGN, the paper establishes the syndrome differentiation criteria of CGN for Chinese and western medicine. Through summarizing the literature on animal models of CGN and making a further analysis, it is found that the CGN models are mainly modeled using rats with the methods of single-factor induction or two-factor induction, and the main manifestation of the disease characteristics is nephritis-related symptoms. The single-factor-induced or two-factor-induced CGN rat models have a high fitting degree with the clinical characteristics in western medicine, but the fitting degree is insufficient with the clinical characteristics in traditional Chinese medicine. In addition, the CGN models with syndromes of traditional Chinese medicine are dominated by Qi deficiency in the spleen and kidney and Qi deficiency in the lung and kidney, while models for Yang deficiency in the spleen and kidney, Yin deficiency in the liver and kidney, and deficiency of both Qi and Yin are slightly insufficient. Therefore,

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it is important to prepare a new and improved animal model of CGN, so that a preclinical model can be provided for the exploration of the pathogenesis of CGN in western medicine and traditional Chinese medicine and its therapeutic research.

[Keywords] chronic glomerulonephritis; fitting degree with clinical characteristics; disease characteristics in western medicine and traditional Chinese medicine; animal model

慢性肾小球肾炎(CG N)是由不同的原因和各种病理体征及其类型共同构成的一种具有自身免疫反应的慢性肾小球疾病^[1]。病情缠绵难愈且易反复,一旦发生病程不可逆,最终可进展至终末期肾病,预后较差,其发病率逐年增加,是继心脑血管疾病、肿瘤之后又一个威胁人类健康的重要疾病^[2-3]。针对CG N,现代医学对其没有特异的治疗办法,主要以控制高血压、降低尿蛋白、改善肾脏微循环等对症为主,但不良反应多,临床疗效不尽人意^[4-5]。中医将慢性肾小球肾炎归属“风水”“肾风”“水肿”“血尿”“腰痛”“虚劳”范畴,对其认识悠久,最早在《黄帝内经·素问·奇病论》论述^[6]。中医认为其为本虚标实证,本虚为肾、脾、肺的虚损,以肾虚为主,标实为湿热瘀血。多以内服方剂,外用中药灌肠、穴位外敷和艾灸等治疗CG N^[7-8]。为深入研究CG N的发病机制及探讨CG N的诊疗方案,现代研究中创建了多种CG N动物模型,而“临床吻合度”为一种评估动物模型模拟临床中医病证的评价方法^[9]。目前CG N制备方法主要以单因素和复合双因素诱导^[10],其诱导的CG N动物模型多数基于西医理念,而缺乏病证结合的中医理念。因此,本文依据CG N中西医临床辨证标准,通过分析归纳现有CG N动物模型,分析现有CG N动物模型的临床吻合度,以期慢性肾小球肾炎病证结合动物模型的建立与完善提供参考。

1 CG N的病因病机

1.1 西医发病机制 CG N被认为与某些免疫性和非免疫性肾脏疾病有关。①体液免疫机制^[11]:抗原与抗体结合形成免疫复合物,免疫复合物的沉积引起肾炎。②细胞介导的免

疫^[12-13]:T淋巴细胞释放的淋巴毒素能够破坏肾小球基底膜,以及吸引单核细胞渗入肾小球引起肾小球损害。③免疫炎症机制^[14]:肾小球细胞可产生许多炎性介质,包括白细胞介素,多肽生长因子,环氧合酶产物和活性氧。这些介质过多产生会损坏肾小球结构和功能。④非免疫性肾病^[15-16]:健康肾的代偿性血清灌注压升高,肾小球毛细血管袢跨膜压滤过压升高和因疾病而长期存在的高血压也可引起肾小球硬化。**1.2 中医病因病机** 中医将CG N归属“风水”“肾风”“水肿”“血尿”“腰痛”“虚劳”范畴^[17]。其病因病机属本虚标实,国医大师张大宁^[18]认为CG N是肾脏疾病,肾虚是发病关键。国家名老中医专家王孟庸教授主张随尿漏出的蛋白精微,即“尿浊”与脾胃亏虚直接相关^[19]。李延教授强调CG N本在肾、标在肺、制在脾的病因病机^[20]。以肾虚为主的“本虚”为主要因素贯穿疾病始终;湿热、瘀血等邪实也存在其不同病理阶段,肾虚、湿热、血瘀三者相合构成其基本病机。

2 CG N疾病的诊断标准

2.1 西医诊断标准 CG N疾病的西医诊断标准根据人民卫生出版社葛均波第9版《内科学》^[21]、《慢性肾小球肾炎》^[22]、《慢性肾脏病早期筛查、诊断及防治指南(2022年版)》^[23]和《内科疾病诊断与疗效标准》^[24],拟定CG N疾病西医诊断标准5条。为量化CG N动物模型与西医诊断标准的临床吻合度,笔者参考动物模型评价新方法^[25],对临床诊断标准进行赋值:临床表现①②③症状较为明显,每项赋值20%;组织病理学为检测金标准,赋值30%;其余各项总赋值10%,共计100%。见表1。

表1 CG N西医诊断标准

Table 1 Western diagnostic criteria for chronic glomerulonephritis

指标分类	表现
临床表现	不同程度的水肿,眼睑及颜面甚至双下肢浮肿,严重者可有胸水、腹水;蛋白尿、血尿、管型尿;具有高血压及贫血貌,唇甲苍白;起病缓慢,病情迁延,时轻时重
常规检查	常规尿液检查有尿蛋白,镜下血尿和/或肾小管尿液;尿比重降低,圆盘电泳主要用于中分子蛋白尿;红细胞为变形红细胞
血液免疫生化检查	内生酞清除率(Ccr)、一氧化氮(NO)水平下降;肌酐(Scr)、尿素氮(BUN)、尿酸(UA)升高;血清降钙素原(PCT)、白细胞介素-6(IL-6)、肿瘤坏死因子- α (TNF- α)水平上升
影像检查	双肾缩小,双肾实质病变
组织病理学	肾活检为系膜增殖性、膜增殖性、膜性肾病或局灶性肾小球硬化症

2.2 中医诊断标准 参照东南大学出版社陈园桃主编的《中医病证诊疗常规》^[26]、《慢性肾小球肾炎的中医辨证论治》^[27]、《慢性肾衰竭中西医结合诊疗指南》^[28]和《中医内科病证诊断疗效标准》^[29],CG N证型分类见表2。为评估CG N动物模型与中医临床诊疗标准的吻合情况,对表2各证型主证归纳总结为:①疲倦、少气乏力、懒言;②颜面浮肿、肢体肿胀;③面色苍白、萎黄无华;④纳少;⑤便溏、泄泻;⑥目睛干涩、视物模糊;⑦尿频。次证归纳总结为:①腰脊酸痛;②畏

寒肢冷;③五心烦热,手足心热;④头晕耳鸣;⑤口干、咽燥、咽部暗红,咽痛;⑥脘腹胀满。根据文献^[25],中医临床诊断标准可分为主证和次证,主证每项赋值10%,次证每项赋值5%,共计100%,见表2。

3 CG N动物模型分析

3.1 CG N模型动物的选择 CG N模型已在多动物中制备成功,以大鼠为主,其次小鼠、兔、犬、绵羊、非人灵长类等^[30]。大鼠在生理学、解剖学、病理学及基因学等与人类相

表2 CGN中医诊断标准

Table 2 Chinese medicine diagnostic criteria for chronic glomerulonephritis

证型	主证	次证	舌脉
脾肾气虚证	疲倦乏力, 浮肿, 纳少, 大便溏薄, 尿频	脘腹胀满, 腰酸酸痛	舌质淡红, 有齿痕, 舌苔薄白, 脉细
肺肾气虚证	颜面浮肿, 肢体肿胀, 疲倦乏力, 面色萎黄, 少气懒言	易感冒, 腰酸酸痛	舌淡、苍白润, 有齿痕, 脉细弱
脾肾阳虚证	全身浮肿, 面色苍白, 纳少, 便溏, 泄泻	畏寒肢冷, 腰脊冷痛或酸痛	舌质淡胖, 边有齿痕, 脉沉偏细或沉迟无力
肝肾阴虚证	目睛干涩, 视物模糊	五心烦热, 手足心热, 头晕耳鸣, 阴干咽燥, 腰酸酸痛	舌红少苔, 脉弦细或细数
气阴两虚证	面色无华, 少气乏力, 浮肿	午后低热, 手足心热, 腰痛, 口干	舌质红或偏红, 苔薄少, 脉细或弱或咽燥或咽部暗红, 咽痛

似,且繁殖快、易操作等优点应用,是建立CGN常用动物。小鼠和兔肾证结合模型较少,犬与绵羊大动物则因饲养条件和操作难易程度等问题应用受限。非人灵长类动物与人极其相似,具有较大的医学前景,但由于饲养成本及伦理限制并未得到广泛应用,但后续动物模型的开发选择非人灵长类更接近于临床。

3.2 CGN造模方法与临床吻合度 CGN动物模型主要分为两类。第一类是通过人工操作来模拟疾病的发作,包括嘌呤霉素肾病、阿霉素肾病模型、阳离子化牛血清白蛋白(C-BSA)肾病模型、Heymann肾炎模型、牛血清白蛋白(BSA)肾炎模型和细胞表面抗原(Thy-1)抗血清肾炎模型等。第二类是“自然疾病模型”,包括Higa/Gddy小鼠免疫球蛋白A(IgA)肾病模型^[31-32]。由于自发突变类型一般由杂交获得,具有高成本和高死亡率的特点,目前在国内应用偏少,因此本文主要讨论第一类CGN动物模型,通过分析模型种类、造模方法、成模机制、模型特征等方面,评估不同CGN动物模型与中西医临床吻合度情况。CGN动物模型与中西医临床病证特点吻合情况见增强出版附加材料^[33-46]。

目前,由于研究的实用性与规范性,CGN动物模型通常需要相关试剂使动物产生免疫反应,常见的药物有嘌呤霉素、阿霉素、牛血清白蛋白(BSA)、阳离子化牛血清白蛋白(C-BSA)等,CGN动物模型的评价指标主要包括行为学表现,动物进食进水量、毛色及是否水肿;病理改变主要是系膜增生,膜性增生,膜性肾病或局灶性肾小球硬化。生化指标主要检测Scr、BUN、UA等。在探讨动物模型的基础上,根据文献^[25]及上述评价标准,将其分为3类:高吻合度(综合吻合度 $\geq 70\%$)、中吻合度(综合吻合度 $50\% \sim 70\%$)和低吻合度(综合吻合度 $\leq 50\%$)。

CGN发病机制有多种,临床分型与病理分型相互交错,目前现有CGN的动物模型都是针对某一发病机制。嘌呤霉素肾炎模型针对微小病变性肾病,西医吻合度低,但模型动物病理变化显著,适用于儿童肾病的研究。阿霉素肾炎模型针对局灶性节段性肾小球硬化,吻合度高,但具有慢性进展性肾损害的特点,与人类进行性肾脏疾病的表现非常相似,适用于研究肾小球硬化性肾病的发病机制和治疗方法。针对膜性肾病的造模方法有两种,一是C-BSA肾病模型,吻合度中。二是Heymann肾炎模型,主动型吻合度高,被动型吻

合度低,虽然其抗体的制作较为复杂,但两种的模型的病理表现与人类膜性肾病表现极为相似,适用于MN的机制及免疫复合物的研究。针对系膜增生性肾小球肾炎有3种,一是BSA肾炎模型与吻合度较高,且该模型试剂易获得,方法简单,较易成功,故近年来应用范围较广。二是Thy-1抗血清肾炎模型,吻合度高,该模型肾炎病变明显,系膜细胞增生显著且持续存在,适用于深入研究以系膜增生为主要特征的肾炎的发病机制,三是IgA肾病模型,吻合度高,用复合改良法造模,是目前IgA肾病中较为可靠,成功率高,且病理、临床指标接近人类IgA肾病的动物模型,值得推广。

4 讨论与展望

CGN起病缓慢且隐匿,在以上对CGN中西医临床诊断标准和动物模型研究中分析可得,目前西医通过临床表现、检查、生化指标联合进行诊断^[47-48],辅助影像学^[49-50]、肾活检来敲定CGN疾病的发生,但只有在肾脏实质改变时才会发现,对于早期CGN的诊断有很大局限性,相较之下,中医在早期诊断慢性肾小球肾炎存在优势^[51],但中医诊断标准受疾病本身的特殊性与主观因素影响,不能如同临床患者那样很好地体现“望”和“切”的诊断,一般通过观察动物毛发、二便、体质量、精神状况和一些行为学测试来作为判断指标,实验动物的证候分型难以与中医的证候分型相吻合。目前来看,制定出科学合理的诊断标准,在理论规范层面上研究出与临床贴合度较高的动物模型是主要研究任务。

中医药动物模型是有效认识疾病病因病机、发展规律以及防治措施的基础^[52],广泛应用于中医药研究领域,病证结合动物模型成为当前动物模型发展的趋势^[53-54]。虽然CGN动物模型的造模方法不断完善,但脾肾气虚、肺肾气虚、脾肾阳虚、肝肾阴虚、气阴两虚等证的病证结合动物模型仍研究较少,而且尚未形成规范、统一的动物模型辨证标准,例如中医主证如目睛干涩、视物模糊、尿频在动物身上无法进行量化,舌脉和病因病机如肾虚、湿热、血瘀没有特别体现,无法真正反映中医治法与疾病证候之间的联系,更不能完全重现疾病发展的整个过程。故在复制动物模型时如何加入中医致病因素,准确地复制人类的病理过程,是该模型未来努力的方向。例如可在吻合度高的BSA肾炎模型基础上,加上强迫游泳、昼夜颠倒、饮食不规律、潮湿环境等使动物烦躁抑郁以更加贴合人类的情志不振,借助气候箱模拟极端环境使

其与中医的六淫邪气相照应来建立中医疾病证候吻合度高的动物模型^[55-57]。中医药是祖国的瑰宝,中药治疗具有多靶点、多途径,价格低廉的优点,现代医学的诊断更加直观,中西医结合相辅相成、扬长避短,期待以中西医结合的方式对慢性肾小球肾炎进一步地研究与实践,以建立贴合中西医临床CGN的动物模型。

[利益冲突] 本文不存在任何利益冲突。

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