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综 述

LRP4抗体阳性的重症肌无力研究进展

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关键词 重症肌无力;低密度脂蛋白受体相关蛋白4;乙酰胆碱受体;肌肉特异性酪氨酸激酶
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自身免疫性疾病是继癌症和心血管疾病后的第三类最为常见的疾病,其在人群中的发生率约为5%,自身免疫性疾病目前仍呈上升趋势,已逐渐成为影响人类健康的主要疾病之一。作为一种最经典的神经系统自身免疫疾病,重症肌无力(myasthenia gravis, MG)是一类异质性的神经肌肉接头(neuromuscular junction, NMJ)突触后膜信号传递障碍的配体门控离子通道病[1]。MG人群发病率为32~64/10万,我国目前MG患者约有60万。该病多青壮年发病,临床表现为眼外肌和/或全身骨骼肌无力,症状起伏迁延。在MG的致病机制方面,已被证实的致病性抗体有两种:抗乙酰胆碱受体(acetylcholine receptor, AChR)抗体和抗肌肉特异性酪氨酸激酶(muscle-specific tyrosine kinase, MuSK)抗体。约有80%的MG患者为AChR抗体阳性的MG(AChR-MG),仅有不足10%的MG患者属于MuSK抗体阳性的MG(MuSK-MG)[2]。这两种抗体介导的MG亚型已被证实存在不同的致病机制、地域分布和临床特点[3-12]。然而,仍有小部分MG患者血清AChR抗体和MuSK抗体均呈阴性,这部分MG被称之为血清双阴性重症肌无力[13]。在这部分血清双阴性重症肌无力患者中,抗低密度脂蛋白受体相关蛋白4(low-density lipoprotein receptor-related protein 4, LRP4)抗体新近被发现,并被证实具有致病性。本文就LRP4抗体阳性的MG(LRP4-MG)的致病机制、流行病学、临床特点以及对药物的反应展开综述。

1 LRP4

LRP4又被称为多表皮生长因子样域7(multiple epidermal growth factor-like domains 7,MEGF7),属于低密度脂蛋白受体家族成员,是由一个跨膜结构、一个长的细胞外N末端以及一个短的细胞内C末端组成的单跨膜蛋白。其中,胞外域由N-末端的8个重复的低密度脂蛋白A类基序以及四个被EGF样模块分隔的含有β-螺旋桨结构域的YWTD模序(即Tyr-Trp-Thr-Asp结构)构成[14-15]。过去一直认为LRP4与脂质代谢、肢体发育以及Wnt信号通路有关[16-19]。近年来研究发现,LRP4是Agrin-LRP4-MuSK-Dok7信号传导通路的重要组成部分[20-21]。它的首个β螺旋桨结构域在与运动神经元释放的集聚蛋白Agrin结合后可激活MuSK,并导致AChR的聚集,进而促进NMJ的形成。值得注意的是,任何导致LRP4结构改变的因素,均可阻断Agrin-LRP4相互作用以及随后的AChR聚集[19, 22]。

2 LPR4抗体的致病机制

Shen等[23]已经证实LRP4抗体可能具有致病性,可诱导MG样表现,相关证据有:(1)用LRP4胞外区免疫小鼠,发现小鼠体内LRP4抗体生成并出现肌无力、疲劳、体质量减轻等症状,重频电刺激检查显示复合肌肉动作电位水平降低。此外,病理研究还发现小鼠NMJ离断、排列紊乱,且缺乏神经支配;(2)神经电生理和形态学研究发现NMJ突触后膜乙酰胆碱受体密度和接头数量减少,突触前膜处突触小泡密度减少以及乙酰胆碱的释放受到破坏;(3)LRP4抗体属于IgG1亚类,可抑制Agrin诱导的MuSK激活和AChR在肌细胞的聚集,并介导了补体依赖的细胞裂解;(4)用来自免疫兔的抗LRP4的IgG注入小鼠可引起MG样症状、复合肌肉动作电位水平下降以及突触传递受损。

3 LPR4抗体的检测及检出率

同AChR抗体和MuSK抗体检测一样,多种方法均可被用于LRP4抗体的检测,如间接荧光免疫法、酶联免疫吸附法、放射免疫沉淀法、荧光免疫沉淀法、细胞荧光免疫染色法等。由于LRP4抗体较低的阳性检出率,目前国际广泛使用并被认可的是具有较高敏感性和特异性的细胞荧光免疫染色法[24]。

由于种族、地域以及抗体检测方法的不同,来

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自全球不同地区的研究，LPR4抗体阳性检出率差别很大，范围约在3%~50%之间。一项来自日本的研究，利用荧光免疫沉淀法对300例AChR抗体阴性的MG患者血清进行检测，结果发现LPR4抗体检出率为3%左右[25]。一项来自美国的多中心研究发现，利用酶联免疫吸附法，在120例双阴性重症肌无力患者中，LRP4抗体检出率为9.2%[26]。Cossins等[20]利用细胞荧光免疫染色法检测，LPR4抗体检出率为8%，研究同时发现在部分MuSK抗体阳性的患者，有部分LRP4抗体亦可呈阳性。而在一项欧洲多中心临床研究中，约10个国家635例双阴性重症肌无力患者血清用细胞荧光免疫染色法检测，LRP4抗体检出率为18.7%(7%~32.7%)。研究还发现，在部分AChR/MuSK-MG患者中，LPR4抗体可与AChR抗体或MuSK抗体相伴随呈现双阳性，而AChR抗体和MuSK抗体同时阳性的MG患者则非常少见[27]。

4 LRP4-MG的临床特征及对治疗的反应

到目前为止，亚洲尚缺乏基于LPR4-MG的多中心临床研究。来自欧美的多项研究结果显示，LRP4-MG男女比例为1:2.5，好发年龄40岁左右，且女性患者发病年龄略小于男性。LRP4-MG起病症状较轻，美国重症肌无力协会(MGFA)临床分型绝大多数为Ⅰ和Ⅱ型，仅有12%的患者为Ⅲ型，3%的为Ⅳ型。在眼肌型MG中，约有20%为LRP4-MG，而AChR-MG约占50%，MuSK-MG极少出现眼肌受累。LRP4-MG极少出现肌无力危象。但须注意的是，AChR抗体/LPR4抗体或MuSK抗体/LPR4抗体双阳性的患者较AChR抗体或MuSK抗体单阳性的MG患者更容易出现肌无力危象。同MuSK-MG一样，LRP4-MG极少伴随胸腺瘤。在治疗方面，LRP4-MG与AChR-MG一样，对常规MG药物反应良好，但不建议对此类患者常规行胸腺手术。考虑到LRP4-MG在病程中亦有再发的可能，因此研究推荐在疾病稳定期仍需使用免疫抑制剂预防再发[27-30]。

5 小结

LPR4是一种可与神经源性蛋白agrin结合的跨膜蛋白，在NMJ的形成以及功能维持方面起到了至关重要的作用。LPR4抗体是一种新近发现的具有致病性的MG相关抗体。与AChR-MG和MuSK-MG相比，LRP4-MG起病症状较轻，多为眼肌型，极少伴随胸腺瘤或出现肌无力危象，对药物治疗的反应良好。考虑到LRP4-MG的发生与种族、地域相关，因此，我国基于LRP4-MG的临床多中心研究亟待进行。

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