·病例报告·

抗MuSK抗体阳性的重症肌无力合并Graves病一例

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【关键词】 重症肌无力； 格雷夫斯病； 受体蛋白质酪氨酸激酶类； 受体,胆碱能； 病例报告

【Key words】 Myasthenia gravis; Graves disease; Receptor protein-tyrosine kinases; Receptors, cholinergic; Case reports

Anti-MuSK antibody positive myasthenia gravis with Graves disease: one case report

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患者 男性,24岁,因视物成双伴双眼上睑下垂22个月、加重6周,于2017年7月7日至河北省保定市第一中心医院就诊。22个月前(2015年9月)无明显诱因出现视物成双,自觉左眼不能外展,习惯性单眼视物,继而出现双眼上睑下垂,眼睑抬举费力,伴多汗、皮肤潮湿和手抖,无视力下降、视野缺损,无头痛、言语不清、张口困难、颈肌无力、肢体无力、感觉异常、吞咽困难和饮水呛咳、肌肉疼痛和肌肉跳动,休息和睡眠后上睑下垂减轻,外院行头部CT检查未见异常,仅予维生素B_1和B_{12}(维生素B_1 100 mg和维生素B_{12} 500 μg肌肉注射1次后改为维生素B_1 10 mg/次、3次/d和维生素B_{12} 500 μg/次、3次/d口服)治疗1个月后无明显改善;16个月前(2016年3月)于外院行新斯的明试验呈阳性,甲状腺功能试验显示甲状腺功能亢进,临床疑诊"重症肌无力,甲状腺功能亢进症",予泼尼松(具体剂量不详)和甲巯咪唑20 mg/d口服,治疗3~4个月症状好转后自行停药;于6周前(2017年5月)双眼上睑下垂症状加重,伴视物成双,无视力下降、视野缺损、构音障碍、肢体无力和呼吸困难等症状。患者自发病以来,精神、睡眠佳,自述平素饮食欠佳,大小便正常,体重无明显变化。既往史、个人史及家族史均无特殊。入院后体格检查:体温36.4 ℃,脉搏72次/min,心率18次/min,血压为110/80 mm Hg(1 mm Hg=0.133 kPa),双侧甲状腺肿大,心、肺、腹部未见明显异常。神经系统检查:神志清楚,语言流利,双侧轻度突眼、上睑下垂、眼裂变小,双侧瞳孔等大、等圆,直径约3 mm,对光反射灵敏,左眼上视可、内收受限(角膜外缘距离内眦4 mm)、外展和下视不能,右眼上视、外展受限(角膜外缘距离外眦3 mm)、内收和下视不能,双眼闭目有力,双侧面纹对称,伸舌居中,双侧软腭抬举正常,咽反射正常,转颈和耸肩有力,四肢肌力和肌张力正常,共济运动和感觉系统正常,腱反射对称,病理征阴性,脑膜刺激征阴性。实验室检查:血尿便常规、血糖、血清糖化血红蛋白(HbA1c)、红细胞沉降率(ESR)、肌酶谱、肿瘤标志物筛查、抗核抗体(ANA)谱、感染五项[甲型肝炎病毒、乙型肝炎病毒、丙型肝炎病毒、梅毒螺旋体(TP)特异性抗体、人类免疫缺陷病毒(HIV)抗体]、IgA、IgG、IgM、补体C3和C4、C反应蛋白(CRP)等均于正常值范围,甲状腺功能试验促甲状腺激素(TSH)<0.005 mU/L(0.27~4.20 mU/L),T_3 5.36 nmol/L(1.20~3.10 nmol/L),T_4 239.10 nmol/L(66~181 nmol/L),游离T_3为27.78 pmol/L(3.10~

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6.80 pmol/L)，游离T_4 > 100 pmol/L(12～22 pmol/L)，抗促甲状腺激素受体(TSHR)抗体为23.72 U/ml(0～30 U/ml)，抗甲状腺过氧化物酶(TPO)抗体为>1000 U/ml(0～30 U/ml)，抗甲状腺球蛋白(TG)抗体315 U/ml(0～30 U/ml)，抗甲状腺微粒体(TM)抗体为385.30 U/ml(0～10 U/ml)。影像学检查：头部MRI检查未见明显异常。胸部CT未见明显异常。心脏彩超显示，心内结构无明显异常；左心室舒张功能和收缩功能正常。甲状腺彩超显示，甲状腺实质回声欠均匀。甲状腺动态显像显示甲状腺肿大，$^{99}Tc^m$摄取不均匀，血流灌注和$^{99}Tc^m$摄取功能未见明显异常。肌电图显示，面神经低频重复神经电刺激(RNS)可见递减现象(刺激频率为1、3和5 Hz时波幅分别下降12%、18%和17%)；左侧尺神经未见明显异常。进一步完善重症肌无力相关抗体检测，血清抗肌肉特异性受体酪氨酸激酶(MuSK)抗体阳性，血清抗乙酰胆碱受体(AChR)抗体阴性。临床诊断为抗MuSK抗体阳性的重症肌无力；Graves病。予溴吡斯的明60 mg/次、3次/d口服(服药初期短暂性出现唾液分泌增多和胃痉挛等不适，自行好转)和泼尼松20 mg/d晨起顿服(每3天增加5 mg/d)。患者共住院12 d，出院时眼肌麻痹症状无明显好转。出院后1个月门诊复查，泼尼松剂量增至60 mg/d晨起顿服，双眼上睑下垂和视物成双明显好转，体格检查：双侧眼裂正常，左眼上视、下视、内收正常，外展受限(角膜外缘距离外眦3 mm)，右眼上视、下视、外展正常，内收受限(角膜外缘距离内眦3 mm)，疲劳试验睁闭眼20次后眼裂无明显减小。

讨　论

本文患者为男性，发病年龄24岁，以眼外肌和上睑提肌功能障碍发病，近2年病程仍以上睑下垂和视物成双为主，故病程进展相对缓慢，临床表现、新斯的明试验和肌电图重复神经电刺激均符合重症肌无力的诊断，激素治疗效果较好。

重症肌无力是由抗AChR抗体介导的、细胞免疫依赖的、补体参与的、累及神经肌肉接头(NMJ)突触后膜的神经肌肉接头传递障碍，从而导致骨骼肌收缩无力的获得性自身免疫性疾病[1]。由于免疫应答的泛化，可以引起自身免疫性疾病重叠发病。重症肌无力常合并自身免疫性甲状腺疾病，如甲状腺功能亢进症和甲状腺功能减退症。文献报道，有1.2%～8.1%的重症肌无力患者可以合并甲状腺功能亢进症[2-3]。甲状腺功能亢进症本身并不直接引起重症肌无力，而是由于甲状腺激素分泌增加，乙酰胆碱分解加速，使乙酰胆碱缺乏，故发生神经肌肉接头传递障碍，从而导致重症肌无力。甲状腺功能亢进症和重症肌无力均是器官特异性自身免疫性疾病，临床常见二者同时或先后共存于同一患者，表明二者可能存在相关联的免疫学机制。此类患者血液中可以检出甲状腺抗体和肌纤维抗体，这些抗体与AChR结合，使其表达下调和部分功能缺失，导致神经肌肉接头传递障碍而出现肌无力[4]。

近年对重症肌无力的发病机制进行大量研究，自身抗体发挥重要作用，如抗AChR抗体、抗Ryanodine受体(RyR)抗体、抗MuSK抗体等[5]。早在2001年，Hoch等[6]即已报告抗MuSK抗体，认为约70%的抗AChR抗体阴性的全身型重症肌无力患者血清中可以检测到抗MuSK抗体。MuSK是神经肌肉接头发育所必需的神经源性蛋白受体，由运动神经元产生，可以诱导AChR聚集于突触后膜；其抗体可以抑制聚集蛋白介导的突触后膜AChR的聚集，从而影响神经肌肉接头传递功能[5]。研究显示，抗MuSK抗体阳性的重症肌无力的发病机制主要是，减少突触后膜AChR聚集，缺乏补体激活，阻断MuSK与其他分子的相互作用，乙酰胆碱酯酶缺乏，突触前膜结构和功能异常等[7]。

抗MuSK抗体阳性的重症肌无力女性多发，占70%以上[3,8-12]；发病年龄较小，通常于40岁前发病，60岁后较少发病，平均发病年龄36～38岁[3,9,12-13]；典型表现为急性发病，数周内进展迅速[3]。临床主要表现为上睑下垂和视物成双，进展迅速，可累及延髓[10]，易发生危象，单纯以眼部症状首发的患者较少，但延髓症状出现率高于抗AChR抗体阳性的重症肌无力患者[3]；而单纯以眼肌麻痹首发的抗MuSK抗体阳性的重症肌无力患者通常2～3周内进展为全身型重症肌无力[3]，但有部分患者以反复上睑下垂和视物成双为唯一症状[14-15]。临床还主要表现为肌肉疼痛、吞咽困难、面部和颈部肌无力且部位较局限，常发生于眼外肌、颈肌和呼吸肌，较少累及四肢肌肉；肌萎缩发生率较高，主要表现为舌肌、咬肌、颞肌、眼轮匝肌和口轮匝肌明显肌萎缩[16-18]。

血清抗MuSK抗体检测可以明确诊断抗MuSK抗体阳性的重症肌无力，因此对于血清抗AChR抗体阴性或血清抗AChR抗体阳性而对治疗反应欠佳的患者应行血清抗MuSK抗体检测。抗MuSK抗体

阳性的重症肌无力患者滕喜龙试验、新斯的明试验和重复神经电刺激阳性率均较低，仅40%～75%的患者滕喜龙试验或新斯的明试验阳性[3,10,12,19-20]，且重复神经电刺激的敏感性较低，尤其是肢体远端肌肉[3,21]。既往研究显示，仅12%～57%的抗MuSK抗体阳性的重症肌无力患者行重复神经电刺激出现波幅明显降低[3,10,12,22]；但是近端肌肉尤其是面肌（眼轮匝肌）重复神经电刺激可以显著提高其诊断灵敏度（75%～85%）[12,23-24]。研究显示，面肌（眼轮匝肌）重复神经电刺激异常而肢体重复神经电刺激正常对抗MuSK抗体阳性的重症肌无力的预测作用优于抗AChR抗体阳性的重症肌无力（$OR=5.200$，95%CI：1.300～20.990；$P=0.020$）[25]。治疗方面，由于抗MuSK抗体阳性的重症肌无力患者的胸腺病理学表现通常正常，极少合并胸腺瘤，因此胸腺切除术效果欠佳；对溴吡斯的明反应较差，常规剂量即可出现不良反应；对糖皮质激素和免疫抑制剂效果较好[26]。

本文患者典型表现为双眼上睑下垂和视物成双，病程中无肌肉疼痛、吞咽困难、面部和颈部肌无力和肌萎缩，血清抗MuSK抗体阳性，同时合并Graves病，有高代谢和交感神经兴奋表现（多汗、皮肤潮湿、手抖等），实验室检查多项甲状腺抗体（抗TPO抗体、抗TG抗体、抗TM抗体）阳性，影像学检查甲状腺弥漫性肿大，抗MuSK抗体阳性的重症肌无力合并Graves病诊断明确，且提示患者存在多个B细胞活化转变为浆细胞而产生自身抗体，从而导致自身免疫性疾病[27]，目前尚未见国内外有相关报道。抗甲状腺抗体与抗MuSK抗体之间的关联性，尚待在今后的临床工作中不断发现与总结。

利益冲突 无

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WFNS Congress Beijing 2019

Time: September 9–12, 2019

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The WFNS Congress Beijing 2019 will be held on September 9–12, 2019 in Beijing, China under the auspices of the World Federation of Neurosurgical Societies (WFNS), which is hosted by the Chinese Medical Doctor Association and Chinese Medical Association.

Founded in 1955, The WFNS is a professional and scientific non-governmental organization comprised of 130 members including 5 continental associations, 119 national or regional neurosurgical societies and 6 affiliate societies. WFNS is the highest academic organization of neurosurgery and the family of all neurosurgeons around the world. The WFNS Congress plays an important role in enhancing medical technology, strengthening academic exchanges and promoting collaborative research and exploration in neurosurgery and related disciplines.

"Glorious Neurosurgery" is the theme of WFNS Congress Beijing 2019. We will hold the opening ceremony on the Great Wall in the golden season. The conference hall is adjacent to the "Bird´s Nest", the main venue of the 2008 Summer Olympics and the 2022 Winter Olympics. Apart from a perfect scientific program, we will work hard to organize a wealth of cultural activities and very interesting tours for you and your companions. We will also invite 150 young neurosurgeons from the developing countries especially along the "Belt and Road" regions to attend the congress free of registration fee, food and accommodation. Furthermore, we will provide international return fares and a month-long clinical training afterwards in Beijing to 50 of them free of charge in food and accommodation.