·神经免疫性疾病·

肢带型肌营养不良症2B型与免疫介导的坏死性肌病临床及影像学差异分析

赵亚雯 王艳莉 王朝霞 张巍 袁云

【摘要】 **目的** 探讨肢带型肌营养不良症2B型(LGMD2B)与免疫介导的坏死性肌病(IMNM)的临床和影像学差异。**方法** 纳入2014年1月至2018年12月收治的LGMD2B型(45例)和IMNM(45例)患者,记录性别、发病年龄、确诊年龄和延误就诊时间;酶耦联法测定血清肌酸激酶水平;英国医学研究理事会6级测定法评价颈屈肌、上肢近端和远端肌力、下肢近端和远端肌力并计算肌力百分比;双大腿MRI评价骨骼肌脂肪浸润和水肿程度。**结果** LGMD2B型患者发病年龄($Z=-3.605$,$P=0.000$)和确诊年龄($Z=-2.757$,$P=0.006$)早于、就诊延误时间长于($Z=-4.749$,$P=0.000$)、血清肌酸激酶水平高于($Z=-2.247$,$P=0.025$)IMNM患者。IMNM患者颈屈肌肌力($Z=-6.320$,$P=0.000$)和肌力百分比($t=-6.320$,$P=0.000$),以及上肢近端肌力($Z=-3.528$,$P=0.000$)和肌力百分比($t=-3.762$,$P=0.000$)低于LGMD2B型患者,而LGMD2B型患者下肢远端肌力($Z=-3.256$,$P=0.001$)和肌力百分比($t=-2.883$,$P=0.004$)低于IMNM患者。LGMD2B型患者双大腿前群肌($Z=-3.119$,$P=0.002$)和后群肌($Z=-2.534$,$P=0.011$)脂肪浸润程度高于IMNM患者,而IMNM患者双大腿后群肌水肿程度高于LGMD2B型患者($Z=-3.887$,$P=0.000$)。**结论** 与IMNM患者相比,LGMD2B型患者发病年龄更早、延误就诊时间更长、下肢远端肌力更差、血清肌酸激酶水平更高、大腿肌肉脂肪浸润程度更严重;而IMNM患者则呈现更为严重的颈屈肌和上肢近端肌无力,以及明显的大腿后群肌水肿。

【关键词】 肌营养不良,肢带型; 多发性肌炎; 坏死; 自身免疫; 肌力; 肌,骨骼; 磁共振成像

Clinical and imaging differences between limb-girdle muscular dystrophy type 2B and immune-mediated necrotizing myopathy

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【**Abstract**】 **Objective** To investigate the clinical and imaging differences between limb-girdle muscular dystrophy type 2B (LGMD2B) and immune-mediated necrotizing myopathy (IMNM). **Methods** Forty-five patients with LGMD2B and 45 patients with IMNM from January 2014 to December 2018 were included. Sex, age of onset, age of diagnosis and time of delay in admission were recorded, and serum creatine kinase (CK) level was measured. Cervical flexion, proximal and distal upper limbs, proximal and distal lower limbs were evaluated by Medical Research Council (MRC) Level 6 and muscle strength percentages were calculated. Skeletal muscle fatty infiltration and edema degree on both thighs were evaluated by MRI. **Results** The onset age ($Z=-3.605$, $P=0.000$) and diagnosis age ($Z=-2.757$, $P=0.006$) of LGMD2B patients were earlier than those of IMNM patients, while the delay time of admission was longer than that of IMNM patients ($Z=-4.749$, $P=0.000$), the serum CK was higher than that of IMNM patients ($Z=-2.247$, $P=0.025$). The muscle strength of neck flexion ($Z=-6.320$, $P=0.000$) and percentage of muscle strength ($t=-6.320$, $P=0.000$), the muscle strengh of proximal upper extremities ($Z=-3.528$, $P=0.000$) and percentage of muscle strength ($t=-3.762$, $P=0.000$) in IMNM patients were lower than those in

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LGMD2B patients, while the muscle strengh of distal lower extremity (Z = - 3.256, P = 0.001) and percentage of muscle strength (t = - 2.883, P = 0.004) in LGMD2B patients were lower than those in IMNM patients. LGMD2B patients had higher muscle fatty infiltration degree in anterior group (Z = - 3.119, P = 0.002) and posterior group (Z = - 2.534, P = 0.011) of thigh muscle than IMNM patients, but IMNM patients had highter thigh muscle edema degree in posterior group than LGMD2B patients (Z = - 3.887, P = 0.000). **Conclusions** Compared with IMNM patients, LGMD2B patients had earlier onset age, longer delay in diagnosis time, worse muscle strength of distal lower extremities, higher serum CK and more obviously thigh muscle fatty infiltration. In IMNM patients, muscle weakness of neck flexion and proximal upper extremities, thigh muscle edema of posterior group were more obvious. These characteristics contribute to the clinical differentiation of the two diseases.

【Key words】 Muscular dystrophies, limb - girdle; Polymyositis; Necrosis; Autoimmunity; Muscle strength; Muscle, skeletal; Magnetic resonance imaging

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Conflicts of interest: none declared

肢带型肌营养不良症2B型(LGMD2B)系*DYSF*基因突变导致的常染色体隐性遗传性肌肉病,主要病理改变呈现骨骼肌肌纤维坏死、再生,伴Dysferlin蛋白缺失。发病高峰年龄为15~25岁,临床主要表现为进行性肢体近端肌无力、肌萎缩,伴不同程度肢体远端肌无力;血清肌酸激酶(CK)水平升高10~50倍[1];骨骼肌MRI可见下肢肌肉不同程度脂肪化伴水肿改变[2]。免疫介导的坏死性肌病(IMNM)是一组以肌纤维坏死、再生为主要病理特点的特发性炎症性肌肉病,多于成年期发病,平均发病年龄约为50岁[3-4],临床主要表现为对称性肢体近端肌无力,血清肌酸激酶水平升高约20倍[5-6],骨骼肌MRI亦可见明显水肿,少数患者还可见双下肢后部骨骼肌明显脂肪化改变[7]。这两种疾病均于成年期发病,具有相似的临床表现、血清学和骨骼肌病理改变,因此,LGMD2B型在临床上易被误诊为炎性肌肉病而延误治疗[8-9]。肌炎特异性抗体测定、基因检测和肌肉组织活检术可资鉴别。本研究对比分析LGMD2B型与IMNM的临床和影像学特点,区分二者的临床差异,以期能够从临床上初步鉴别诊断两种疾病。

对象与方法

一、研究对象

选择2014年1月至2018年12月在北京大学第一医院神经内科门诊或住院治疗的LGMD2B型和IMNM患者各45例。(1)LGMD2B组:45例患者均经骨骼肌组织活检证实肌纤维坏死和再生,Dysferlin蛋白检测呈阴性;经基因检测证实*DYSF*基因纯合或复合杂合突变;排除以腓肠肌萎缩或无力发病且临床考虑为Miyoshi远端型肌营养不良症的病例。(2)IMNM组:45例患者均经骨骼肌组织活检证实肌纤维坏死和(或)再生,Dysferlin蛋白检测呈阳性;血清肌炎特异性抗体测定可见13例信号识别颗粒(SRP)抗体呈强阳性、9例3-羟基-3-甲基戊二酸单酰辅酶A还原酶(HMGCR)抗体强阳性、2例OJ抗体呈弱阳性、2例KU抗体呈弱阳性和1例PL-7抗体呈弱阳性,其余18例血清抗体检测均呈阴性。本研究经北京大学第一医院临床研究伦理委员会审核批准(审批号:2012-542),所有患者及其家属对研究项目和检测方法知情并签署知情同意书。

二、研究方法

1. 临床资料采集 (1)血清肌酸激酶检测:初诊时抽取患者外周静脉血3 ml,采用酶耦联法测定血清肌酸激酶(正常参考值:25~195 U/L)。(2)肌力测评:采用英国医学研究理事会(MRC)6级测定法分别评价颈屈肌肌力、上肢近端肌力(肩内收、肩外展、屈肘、伸肘)和远端肌力(伸腕、屈腕、握力)、下肢近端肌力(屈髋、髋内收、髋外展、屈膝、伸膝)和远端肌力(足背伸、跖屈)。0级,肌肉无收缩;1级,能够触知肌腱收缩,但不能产生关节运动;2级,有关节运动,但不能克服地心引力运动;3级,能克服地心引力运动,但不能做阻力运动;4级,能做阻力运动,但较正常肌力弱;5级,肌力正常,运动自如。(3)肌力百分比计算:计算公式为肌力百分比(%)=肌力总和/(检查部位总和×5)×100%[10-11]。

2. 大腿MRI检查 本研究有67例患者行双侧臀部和双大腿骨骼肌MRI检查,LGMD2B组33例、

表1　LGMD2B组与IMNM组患者肌力和肌力百分比的比较

Table 1.　Comparison of muscle strength and percentage of muscle strength between LGMD2B group and IMNM group

组别	例数	颈屈肌		上肢近端		上肢远端		下肢近端		下肢远端	
		肌力评分[$M(P_{25},P_{75})$]	肌力百分比($\bar{x}\pm s$,%)	肌力评分[$M(P_{25},P_{75})$]	肌力百分比($\bar{x}\pm s$,%)	肌力评分[$M(P_{25},P_{75})$]	肌力百分比($\bar{x}\pm s$,%)	肌力评分[$M(P_{25},P_{75})$]	肌力百分比($\bar{x}\pm s$,%)	肌力评分[$M(P_{25},P_{75})$]	肌力百分比($\bar{x}\pm s$,%)
LGMD2B组	45	5.00 (5.00,5.00)	96.40± 7.65	5.00 (4.75,5.00)	94.80±11.40	5.00 (5.00,5.00)	99.40±3.09	4.40 (4.00,5.00)	87.90±12.26	5.00 (4.50,5.00)	92.70±11.23
IMNM组	45	3.00 (3.00,4.00)	68.90±21.73	4.50 (4.00,5.00)	87.60±11.14	5.00 (5.00,5.00)	99.70±1.97	4.40 (4.20,4.80)	88.70± 8.53	5.00 (5.00,5.00)	97.30± 8.79
Z值		-6.320	-6.320	-3.528	-3.762	-2.400	-2.571	-0.270	-0.367	-3.256	-2.883
P值		0.000	0.000	0.000	0.000	0.559	0.556	0.788	0.713	0.001	0.004

LGMD2B，limb-girdle muscular dystrophy type 2B，肢带型肌营养不良症2B型；IMNM，immune-mediated necrotizing myopathy，免疫介导的坏死性肌病。The same for Table 2 below

IMNM组34例，采用美国GE公司生产的Sigma 3.0T MRI扫描仪，扫描序列主要包括T_1WI[重复时间(TR)480～620 ms、回波时间(TE)8 ms]和短时间反转恢复(STIR)序列[重复时间6000～6200 ms、回波时间70 ms、反转时间(IT)180 ms]，扫描视野(FOV)36 cm×38 cm，矩阵256×256，层厚为5 mm、层间距1 mm。分别于臀大肌层面和大腿中部层面选取大腿骨骼肌前群(股直肌、股外侧肌、股中间肌、股内侧肌)、内侧群(缝匠肌、股薄肌、长收肌)和后群(臀大肌、大收肌、股二头肌长头、半腱肌、半膜肌)，由两位相互独立的神经内科医师根据改良Mercuri评分标准[12]对骨骼肌脂肪浸润程度和水肿程度进行评价，如果同一例患者双侧同一肌肉评分不同，则取双侧平均值。双侧不对称受累定义为双侧半定量评分相差≥2分。通过横断面T_1WI序列对脂肪浸润程度进行评分：1分，点状高信号病灶；2分，散在高信号病灶，病灶不融合，受累病灶<肌容积的30%；3分，高信号病灶有小片状融合，受累病灶占肌容积的30%～60%；4分，大片状融合高信号病灶，受累病灶>肌容积的60%；5分，终末期改变，骨骼肌呈弥漫性高信号。横断面STIR序列进行水肿程度评分：1分，点状高信号病灶，病灶不融合；2分，信号轻度升高，骨骼肌内散在或小片状高信号病灶，<肌容积的50%；3分，信号明显升高，骨骼肌内散在或小片状高信号病灶，<肌容积的50%；4分，信号轻度升高，骨骼肌内大片状高信号病灶，≥肌容积的50%；5分，信号明显升高，骨骼肌内大片状高信号病灶，≥肌容积的50%。分别计算每块肌肉的脂肪浸润和水肿评分，再对双大腿骨骼肌前群、内侧群和后群肌肉的脂肪浸润和水肿评分进行加和，计为双大腿骨骼肌脂肪浸润和水肿评分。

3.统计分析方法　采用SPSS 22.0统计软件行数据处理与分析。计数资料以相对数构成比(%)或率(%)表示，采用χ^2检验。通过Kolmogorov-Smirnov(K-S)法行正态性检验，呈正态分布的计量资料以均数±标准差($\bar{x}\pm s$)表示，采用两独立样本的t检验；呈非正态分布的计量资料以中位数和四分位数间距[$M(P_{25},P_{75})$]表示，行Mann-Whitney U检验。等级资料采用Mann-Whitney U检验。以$P\leqslant 0.05$为差异具有统计学意义。

结　果

LGMD2B组男性18例，女性27例；发病年龄为12～54岁、中位值25(17,31)岁，确诊年龄为13～65岁、中位值28(20,39)岁；就诊延误时间为0.25～25.00年，中位时间3(1,6)年。IMNM组男性15例，女性30例；发病年龄为2～69岁、中位值为46(27,56)岁，确诊年龄6.00～69.30岁、中位值47.00(28.00,57.70)岁；就诊延误时间0.04～5.00年，中位时间1.00(0.50,1.20)年。两组患者一般资料比较，LGMD2B组患者发病年龄($Z=-3.605$，$P=0.000$)和确诊年龄($Z=-2.757$，$P=0.006$)早于、就诊延误时间长于($Z=-4.749$，$P=0.000$)IMNM组，而性别差异无统计学意义($\chi^2=0.000$，$P=0.833$)。

IMNM组患者颈屈肌肌力($P=0.000$)和肌力百分比($P=0.000$)，以及上肢近端肌力($P=0.000$)和肌力百分比($P=0.000$)均低于LGMD2B组，而LGMD2B组患者下肢远端肌力($P=0.001$)和肌力百分比($P=0.004$)则低于IMNM组，其余骨骼肌肌力和肌力百分比组间差异无统计学意义(均$P>0.05$，表1)。LGMD2B组患者血清肌酸激酶水平为949～38 450 U/L、中位值5584(4000,11 343)U/L，IMNM

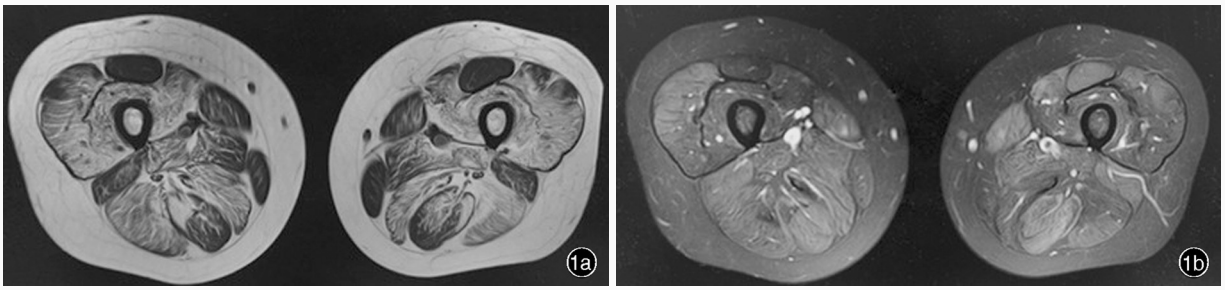

图1 男性LGMD2B型患者，30岁。双大腿MRI检查所见 1a 横断面T_1WI显示脂肪浸润，以前群肌和后群肌明显 1b 横断面STIR序列显示各肌群弥漫性轻度水肿

Figure 1 A 30-year-old male patient was diagnosed as LGMD2B. Thigh MRI findings Axial T_1WI showed fatty infiltration of thigh muscles, with significant anterior and posterior mass muscles (Panel 1a). Axial STIR showed diffuse mild edema (Panel 1b).

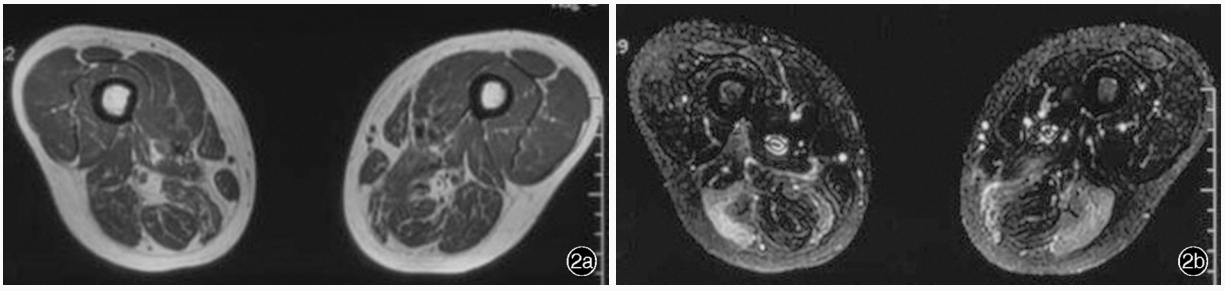

图2 女性IMNM患者，47岁。双大腿MRI检查所见 2a 横断面T_1WI可见以大腿后群肌为主的脂肪浸润 2b 横断面STIR序列可见以大腿后群肌为主的中至重度水肿

Figure 2 A 47-year-old female patient was diagnosed as IMNM. Thigh MRI findings Axial T_1WI showed fatty infiltration of thigh muscles, with significant posterior mass muscles (Panel 2a). Axial STIR showed moderate to severe edema of thigh muscles, with significant posterior mass muscles (Panel 2b).

表2 LGMD2B组与IMNM组患者双大腿骨骼肌脂肪浸润和水肿评分的比较[$M(P_{25},P_{75})$]

Table 2. Comparison of skeletal muscle fatty infiltration and edema scores between LGMD2B group and IMNM group [$M\ (P_{25},\ P_{75})$]

组别	例数	前群肌		内侧群肌		后群肌	
		脂肪浸润	水肿	脂肪浸润	水肿	脂肪浸润	水肿
LGMD2B组	33	2.00(1.00,3.25)	1.50(1.00,2.25)	1.30(0.67,2.00)	1.00(0.67,1.67)	2.60(1.80,3.20)	1.20(0.60,1.80)
IMNM组	34	0.88(0.31,1.40)	1.75(0.75,2.20)	1.33(0.75,2.30)	1.00(0.33,1.30)	0.70(0.40,1.20)	2.50(1.70,3.40)
Z值		-3.119	-1.262	-1.947	-0.841	-2.534	-3.887
P值		0.002	0.207	0.052	0.400	0.011	0.000

组患者血清肌酸激酶为201～17 665 U/L、中位值5100(2141,7666) U/L；组间差异具有统计学意义($Z=-2.247$,$P=0.025$)。

33例LGMD2B型患者双大腿MRI检查可见以前群肌和后群肌显著的轻至中度脂肪浸润，伴弥漫性轻度水肿(图1)。34例IMNM患者双大腿MRI检查以后群肌水肿最为明显，但脂肪化程度较轻(图2)。LGMD2B型患者双大腿前群肌($P=0.003$)和后群肌($P=0.011$)脂肪浸润程度高于IMNM患者，而IMNM患者双大腿后群肌水肿程度低于LGMD2B型患者($P=0.000$)，其余肌群脂肪浸润和水肿程度组间差异无统计学意义(均$P>0.05$，表2)。

讨 论

本研究LGMD2B型和IMNM患者均以女性多见[60%(27/45)和66.67%(30/45)]，与Miller等[4]和Hengstman等[13]报告的IMNM在女性中更有发病优势相一致，但并未发现两种疾病存在性别差异。既往研究显示，LGMD2B型患者发病年龄约25岁[1]；IMNM多于成年期发病，发病年龄约40岁[3]。本研究LGMD2B型患者中位发病年龄为25(17,31)岁，早于IMNM患者的46(27,56)岁。LGMD2B型患者通常呈隐匿发病，故就诊延误时间较长[14-16]；IMNM则以急性或亚急性发病更为常见，就诊较早[17]。本

研究LGMD2B型患者中位诊延误时间为3(1,6)年，长于IMNM患者的1.00(0.50,1.20)年。上述研究结果提示发病早且病程长者更倾向于LGMD2B型。

本研究LGMD2B型和IMNM患者在肢体不同部位的肌力百分比和肌力下降程度存在明显差异，LGMD2B型患者主要表现为下肢远端肌力下降且病情更为严重，与既往文献报道相一致[14,16]，而IMNM患者以颈屈肌和上肢近端肌力下降为主且更严重。既往文献报道，IMNM患者大多表现为以四肢近端为主的肌无力，颈屈肌受累多见[13,18-19]。国外研究显示，约78%的IMNM患者存在颈屈肌无力[3]，而国内仅发现约59.65%的IMNM患者存在颈屈肌无力[6]。本研究LGMD2B型患者亦呈现颈屈肌和四肢近端肌力下降但下降程度低于IMNM患者的特点，而四肢远端肌力下降程度高于IMNM患者，提示上肢近端肌无力轻微而下肢远端肌无力严重的患者更倾向于LGMD2B型。研究显示，IMNM患者血清肌酸激酶水平显著升高[18-19]。本研究LGMD2B型患者血清肌酸激酶水平明显高于IMNM患者，且部分IMNM患者病程中肌酸激酶水平可恢复正常，推测可能由于肌纤维坏死程度较轻或肌纤维坏死程度过重、残留功能肌纤维较少，也可能是由于病情处于相对静止期[3]。因此，结合更高水平的血清肌酸激酶，可进一步支持LGMD2B型的诊断。

上述临床表现的差异性亦可在影像学上得到验证，本研究双大腿MRI显示两组患者骨骼肌脂肪浸润和水肿程度，以及分布范围存在差异，LGMD2B型患者骨骼肌脂肪浸润主要见于前群肌和后群肌、肌肉水肿主要见于前群肌，与既往研究相近[2,20-21]。亦有相关研究显示，脂肪浸润程度可用于评估LGMD2B型疾病进展[22]。IMNM患者骨骼肌脂肪浸润和水肿均以大腿后群肌常见，与Suzuki等[23]的研究结果相一致。结合既往多项研究结果[24-26]，我们认为双下肢近端肌肉水肿与IMNM的疾病活动性密切相关，是评估IMNM疾病活性的可靠指标，而出现大腿前群肌明显脂肪浸润应首先考虑LGMD2B型的可能。

综上所述，LGMD2B型和IMNM这两种以肢带肌无力为主要表现的肌肉病存在明显的临床和影像学差异，前者具有更早的发病年龄、更长的病程、更差的下肢远端肌力、更高的血清肌酸激酶水平，以及更严重的大腿前群肌和后群肌脂肪化，后者则以颈屈肌和上肢近端肌无力症状更为严重，以及大腿后群肌水肿更明显，对于临床鉴别诊断两种疾病具有重要意义。

利益冲突 无

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·小词典·

中英文对照名词词汇（二）

多发性硬化 multiple sclerosis（MS）

多甲藻黄素叶绿素蛋白 peridinin-chlorophyll-protein（PerCP）

二辛可宁酸 bicinchoninic acid（BCA）

^{18}F-氟比他班 ^{18}F-florbetaben（FBB）

辅助性T细胞 helper T cell（Th）

复发-缓解型多发性硬化 relapse-remitting multiple sclerosis（RRMS）

副肿瘤性小脑变性 paraneoplastic cerebellar degeneration（PCD）

富亮氨酸胶质瘤失活蛋白 leucine-rich glioma-inactivated 1（LGI1）

改良Rankin量表 modified Rankin Scale（mRS）

干燥综合征A型抗体 A type Sjögren's syndrome antibody（SSA）

干燥综合征B型抗体 B type Sjögren's syndrome antibody（SSB）

甘油三酯 triglycerides（TG）

高密度脂蛋白胆固醇 high-density lipoprotein cholesterol（HDL-C）

工具性日常生活活动能力 intellect activities of daily living（IADL）

谷氨酸脱羧酶 glutamic acid decarboxylase（GAD）

谷氨酰胺转胺酶 transglutaminase（TG）

国际多发性硬化国际学会联合会 International Federation of Multiple Sclerosis Societies（IFMSS）

国际多发性硬化协会 International Multiple Sclerosis Genetics Consortium（IMSGC）

国际儿科多发性硬化研究小组 International Pediatric Multiple Sclerosis Study Group（IPMSSG）

国际运动障碍学会 Movement Disorder Society（MDS）

核因子-κB nuclear factor-kappa B（NF-κB）

核周抗中性粒细胞胞质抗体 perinuclear antineutrophil cytoplasmic antibody（pANCA）

红细胞沉降率 erythrocyte sedimentation rate（ESR）

化学发光免疫分析 chemiluminescence immunoassay（CIA）

肌醇需求酶1 inositol-requiring enzyme 1（IRE1）