·临床研究·

晚发型线粒体脑肌病伴高乳酸血症和卒中样发作临床特点

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【摘要】 **目的**　总结10例晚发型线粒体脑肌病伴高乳酸血症和卒中样发作(MELAS)患者的临床、病理及基因突变特点。**方法与结果**　回顾分析2007年1月至2018年12月共10例晚发型MELAS患者的临床资料,8例患者行骨骼肌组织活检术。聚合酶链反应-限制性片段长度多态性和线粒体DNA(mtDNA)全长测序法进行mtDNA突变筛查;焦磷酸测序法检测部分患者血液m.3243A>G突变比例。结果显示,10例患者首次脑卒中样发作的年龄为40~67岁,其主要表现包括癫痫发作、失语、头痛、痴呆、精神障碍、肢体轻瘫及视力下降,既往糖尿病5例、神经性耳聋6例、高血压3例、脑梗死2例。6例患者有母系遗传的糖尿病家族史,2例有MELAS家族史。辅助检查可见6例有高脂血症,6例有颈动脉粥样硬化,1例有右颈内动脉及大脑中动脉狭窄。头部MRI显示累及1个或多个脑叶的皮质病变,4例同时存在脑干及基底节区多发缺血灶。7例肌肉组织活检发现破碎红纤维及琥珀酸脱氢酶深染血管,1例未见明显异常。基因分析显示,10例患者均携带mtDNA突变,9例为m.3243A>G突变,1例为m.10191T>C突变。7例m.3243A>G突变患者血液中突变比例为9%~33%。**结论**　晚发型MELAS患者的临床表型与经典型患者无明显差异,但发病年龄晚,并可合并多种脑血管危险因素及大动脉粥样硬化。m.3243A>G突变为本组晚发型MELAS患者的热点突变,但血液中突变比例较低。

【关键词】 MELAS综合征;　晚发性障碍;　DNA,线粒体;　突变

Clinical features of the late-onset mitochondrial encephalomyopathy with lactic acidosis and stroke-like episodes

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【**Abstract**】 **Objective**　To summarize the clinical, pathological and genetic features of 10 patients with late-onset mitochondrial encephalomyopathy with lactic acidosis and stroke-like episodes (MELAS). **Methods and Results**　The clinical data of 10 patients with late-onset MELAS were retrospectively analyzed from January 2007 to December 2018. Muscle biopsy was performed in 8 cases. Polymerase chain reaction-fragment length polymorphism (PCR-RFLP) analysis and whole sequencing of mitochondrial DNA (mtDNA) were used to screen mtDNA mutations, and the mutation load of m.3243A>G in blood was detected by pyrophosphate sequencing. The onset age of the first stroke-like episodes were 40–67 years old in all patients. The main manifestations included epilepsy, aphasia, headache, dementia, mental disorder, limb paralysis and visual impairment. Past history revealed 5 cases with diabetes mellitus, 6 with deafness, 3 with hypertension and 2 with stroke. Six patients had a family history of maternally inherited diabetic mellitus, and 2 had a family history of MELAS. Laboratory examination revealed 6 cases with hyperlipidemia, 6 with carotid atherosclerosis, 1 with stenosis of right internal carotid artery and middle cerebral artery. Brain MRI showed cortex lesions involving one or more lobes in all patients, and 4 cases also had multiple infarctions in brainstem and basal ganglia. Muscle biopsy demonstrated ragged red fiber

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(RRF) and strongly succinate dehydrogenase-stained vessels (SSVs) in all of 8 patients except one. Genetic analysis identified 9 cases with m.3243A > G, and 1 with m.10191T > C mutation. The blood mutation load of m.3243A > G was 9%–33% in 7 cases. **Conclusions** The clinical phenotype of patients with late-onset MELAS was not significantly different from that of typical patients. However, the age of onset in late-onset MELAS was late, and it could be complicated with a variety of cerebrovascular risk factors and atherosclerosis. The hotspot mutation of this group of late-onset MELAS patients was m.3243A > G, but the mutation rate in blood was low.

【Key words】 MELAS syndrome; Late onset disorders; DNA, mitochondrial; Mutation
Conflicts of interest: none declared

线粒体脑肌病伴高乳酸血症和卒中样发作(MELAS)是常见的线粒体脑肌病之一,具有多系统受累的特点,常见的症状有脑卒中样发作、头痛、癫痫、认知功能减退、糖尿病、耳聋、运动不耐受、身材矮小及多毛等。骨骼肌活检可见特征性破碎红纤维(RRF)和(或)琥珀酸脱氢酶深染血管(SSVs)。80%以上的患者存在线粒体DNA(mtDNA)3243A > G突变[1]。脑卒中样发作是MELAS的核心症状,表现为突发的偏盲/皮质盲、失语、偏瘫及精神症状,头部MRI显示为顶、枕、颞叶交界区大片长T_2信号。经典型MELAS患者在40岁之前出现脑卒中样发作症状[2],仅1%~6%的患者40岁以后发病,称之为晚发型MELAS,临床相对罕见,仅见个案报道[3-16]。因临床医师对晚发型患者的认识程度不够,导致患者从就诊至确诊的时间明显延长。因此,我们总结10例晚发型MELAS患者的临床、病理及基因突变特点,探讨该类型患者的疾病发展规律。

临床资料

一、病例选择

1. 纳入与排除标准 (1)符合2012年Yatsuga等[17]提出的MELAS诊断标准:A临床表现符合脑卒中样发作特点,①头痛伴呕吐。②癫痫发作。③偏瘫。④皮质盲或偏盲。⑤头部CT和(或)MRI证实颅内有局灶的急性病变。B有线粒体功能障碍证据,①静息血浆和(或)脑脊液乳酸≥2 mmol/L,或者线粒体相关酶活性缺乏。②肌肉活检提示线粒体功能障碍,如出现RRF、SSVs或细胞色素C氧化酶(COX)阴性肌纤维,或者电子显微镜显示肌纤维内异常线粒体聚集。③存在可以导致MELAS的致病性mtDNA突变。确诊MELAS需要至少同时满足A项中的2项以及B项中的2项标准。(2)首次脑卒中样发作的年龄≥40岁。(3)临床资料完整。(4)排除临床以皮质病变为主但骨骼肌病理学检查及mtDNA基因检测均无阳性发现的患者。(5)排除首次脑卒中样发作年龄<40岁的患者。(6)排除临床资料不完整的患者。(7)本研究经北京大学第一医院道德伦理委员会审核批准,所有患者对各项检查项目均知情同意并签署知情同意书。

2. 一般资料 选择2007年1月至2018年12月在北京大学第一医院神经内科确诊的晚发型MELAS患者共10例,其中男性1例,女性9例。就诊时年龄45~67岁,平均年龄52岁,首次脑卒中样发作年龄40~67岁,平均年龄50岁,脑卒中样发作次数共13次。此10例患者分别来自无血缘关系的不同家庭。

二、临床特点

1. 临床表现 本组10例晚发型MELAS患者主要临床表现有癫痫发作6例、感觉性失语6例、头痛5例、认知功能障碍3例、意识障碍3例、头晕3例、精神障碍2例、肢体轻瘫2例、视力下降1例、听力减退1例。既往患糖尿病5例,神经性耳聋6例,高血压病3例,丘脑梗死1例,脑干梗死1例,癫痫1例(表1);长期吸烟1例,身材矮小3例。6例患者存在母系遗传的糖尿病家族史。2例患者在发病前其子女已被诊断为MELAS。

2. 辅助检查 实验室检查:本组有9例患者肌酸激酶(CK)正常,1例(例5)轻度升高至246 U/L(25~170 U/L);血脂升高者6例(例2、例3、例6、例7、例8、例9),其中甘油三酯(TG)1.72~2.91 mmol/L(<1.70 mmol/L),总胆固醇(TC)5.39~6.38 mmol/L(<5.20 mmol/L),低密度脂蛋白胆固醇(LDL-C)为3.94~4.14 mmol/L(<3.40 mmol/L),正常者4例。影像学检查:头部MRI显示脑卒中样发作急性期病灶主要累及1个或者多个脑叶的皮质肿胀以及皮质下水肿(图1a),各脑叶受累次数分别为:颞叶9次,枕

表1 10例晚发型MELAS患者的临床、病理学资料及基因突变分析

Table 1. Clinical, pathological data and mtDNA mutation analysis of 10 patients with late-onset MELAS

序号	性别	年龄（岁）	SLE年龄（岁）	SLE表现	既往史	家族史	头部MRI病灶部位	颈动脉超声	头部MRA	骨骼肌病理	突变基因（突变比例）
1	女性	45	40	头痛、反应迟钝、癫痫发作	—	糖尿病	右侧额颞叶	/	/	RRF、SSVs	m.3243A>G（13%）
			45	精神异常、感觉性失语、听力减退			双侧颞叶	/	/		
2	女性	46	45	癫痫发作、偏头痛、眩晕、发热、意识障碍	糖尿病、缺血性卒中	糖尿病	双侧枕叶、脑干梗死；双侧基底节区及侧脑室旁缺血灶	斑块	—	RRF、SSVs	m.3243A>G（/）
3	女性	46	46	眩晕、头痛、感觉性失语、轻偏瘫、反应迟钝、癫痫发作	糖尿病、高血压	糖尿病	左侧颞顶枕叶、右侧小脑	斑块	右颈内动脉及右大脑中动脉狭窄	/	m.3243A>G（9%）
4	女性	46	46	感觉性失语、精神异常、头痛	耳聋、癫痫	MELAS	左侧颞叶、基底节区缺血灶	/	/	RRF、SSVs	m.3243A>G（33%）
5	女性	58	51	癫痫发作、痴呆	糖尿病、耳聋	糖尿病	右侧额叶	/	/	/	m.3243A>G（20%）
			58	意识障碍、糖尿病酮症酸中毒			双侧颞顶叶、右侧枕叶	/	/		
6	女性	52	52	感觉性失语、癫痫发作、意识障碍	糖尿病、耳聋	糖尿病、MELAS	左侧颞顶枕叶、左侧丘脑	—	—	RRF、SSVs	m.3243A>G（16%）
7	女性	67	67	感觉性失语、昏迷	耳聋、高血压	—	左侧颞枕叶伴出血，双侧放射冠、左侧基底节区缺血灶	斑块	—	RRF、SSVs	m.3243A>G（16%）
8	女性	49	47	头痛、感觉性失语、轻偏瘫	耳聋	耳聋、糖尿病	左侧颞叶、左侧丘脑	斑块	—	RRF、SSVs	m.3243A>G（/）
9	男性	53	50	头晕、视物不清	糖尿病、耳聋、高血压、缺血性卒中	—	左侧颞枕叶；右侧基底节区软化灶	斑块	—	RRF、SSVs	m.3243A>G（15%）
10	女性	53	53	癫痫持续状态	—	—	左侧额叶	斑块	—		
			53	肢体麻木、癫痫持续状态	—	—	右侧额叶、左侧顶枕叶、左侧丘脑、右侧小脑	/	/	—	m.10191T>C

—，no abnormal，无异常；/，unchecked，未检测。SLE，stroke-like episodes，脑卒中样发作；RRF，ragged red fiber，破碎红纤维；SSVs，strongly succinate dehydrogenase-stained vessels，琥珀酸脱氢酶深染血管；MELAS，mitochondrial encephalomyopathy with lactic acidosis and stroke-like episodes，线粒体脑肌病伴高乳酸血症和卒中样发作

叶7次，顶叶4次，额叶4次，丘脑3次，小脑2次。有4例患者同时合并脑干、基底节区或放射冠区的多发缺血灶（图1b），1例患者有病灶内少量出血。7例患者行头部MRA检查，1例存在右颈内动脉及大脑中动脉狭窄，狭窄程度约50%，6例正常。超声检查：7例患者行颈动脉超声，其中6例存在动脉粥样硬化斑块，1例无异常。骨骼肌病理学检查：共8例患者获得其知情同意后行肱二头肌组织活检术，HE染色显示肌束内结缔组织无明显增生，肌间小血管壁无明显增厚，血管周围无炎性细胞浸润和异常物质沉积，肌纤维排列紧密，可见个别小圆状萎缩肌纤维，未见肥大、坏死、再生肌纤维；改良Gomori三色（MGT）染色可见个别RRF。油红O（ORO）染色显示破碎样肌纤维内脂肪滴轻度增多。高碘酸-雪夫（PAS）染色可见破碎肌纤维缺乏糖原。其中7例可观察到典型RRF（图2a）、COX阴性肌纤维及SSVs（图2b），符合线粒体病的病理改变特点；1例未见典型病理改变。mtDNA突变检测：采用聚合酶链反应-限制性片段长度多态性（PCR-RFLP）法对所有患者进行mtDNA热点突变筛查，主要包括3243A>G、8344 A>G及8993T>C（G）突变；采用焦磷酸测序法测定血液中3243A>G突变的比例；对未见上述位点突变者，进一步应用第二代测序技术（NGS）行mtDNA全长序列检测。结果显示，10例患者中9例存在m.3243A>G突变，其中有7例患者经焦磷酸测序法检测其血液中的突变比例为9%～33%；另1例患者未检测到上述突变，该例患者的骨骼肌活检亦无典型线粒体病改变，进一步提取该例患者的肌肉组织DNA，进行mtDNA NGS测序，发现其存在致病性m.10191T>C突变。

讨 论

本研究中的10例患者均经骨骼肌病理和基因检查明确诊断，首次脑卒中样发作均在40岁以后，与1992年Hirano等[2]提出的40岁之前出现脑卒中样发作的诊断标准不同，我们将其称之为晚发型MELAS。目前文献所报道的晚发型MELAS患者的发病年龄均超过40岁，最大为80岁[12]，仅1例为

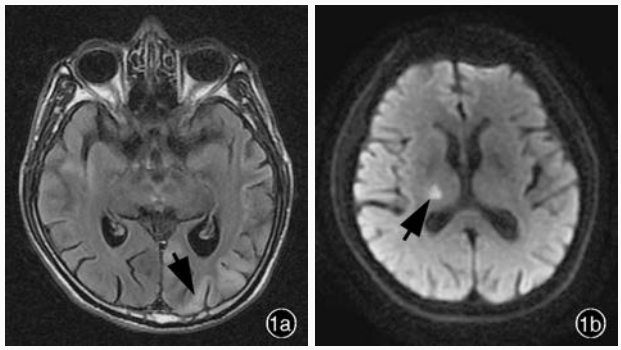

图1　例9患者，男性，53岁，先后被诊断为急性缺血性卒中及MELAS，头部MRI检查所见　1a　横断面T_2-FLAIR成像显示左侧颞枕叶高信号（脑卒中样发作急性期，箭头所示）　1b　横断面DWI显示右侧丘脑急性梗死灶（箭头所示）

Figure 1　Brain MRI findings of Case 9　A 53-year-old male patient was diagnosed as acute ischemic stroke and MELAS successively.　Axial T_2-FLAIR disclosed hyperintensity in the left temporal and occipital lobes (the acute stage of stroke-like episodes; arrow indicates, Panel 1a). Axial DWI revealed acute infarction of right thalamus (arrow indicates, Panel 1b).

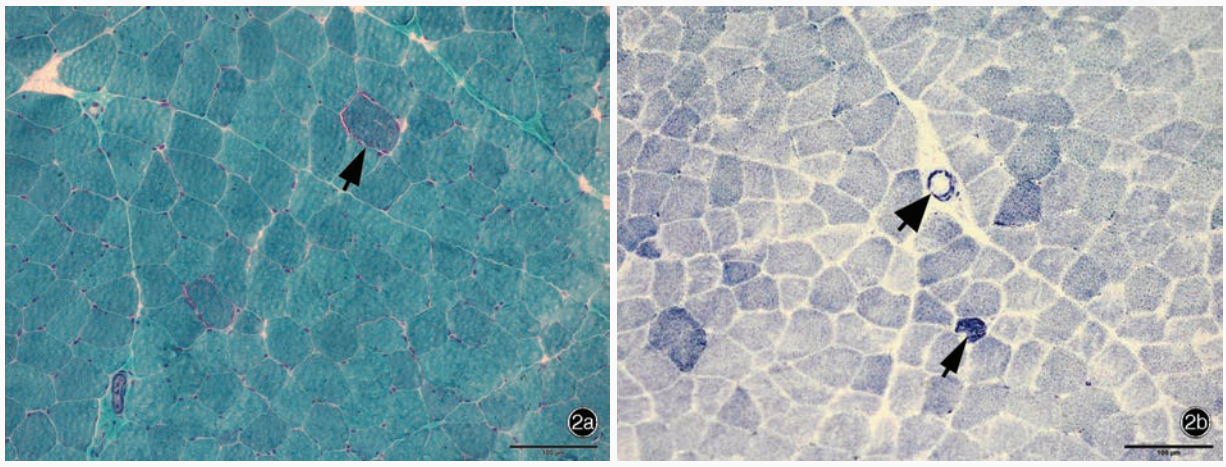

图2　例9患者肌肉组织活检所见　×200　2a　肌束内可见RRF（箭头所示）　改良Gomori三色染色　2b　肌束内可见破碎蓝纤维（细箭头所示）和SSVs（粗箭头所示）　SDH染色

Figure 2　Muscle biopsy of Case 9　×200　RRF was observed in the muscle bundle (arrow indicates).　MGT staining　The ragged blue fibers (thin arrow indicates) and SSVs (thick arrow indicates) could be seen.　SDH staining

36岁发病[18]。由于脑卒中样发作是诊断MELAS的必备条件，因此，在本研究中我们将MELAS的发病年龄定义为首次脑卒中样发作的年龄，而非糖尿病、耳聋等其他症状出现的年龄[18]。本组患者主要的临床表现有脑卒中样发作、癫痫发作、头痛、失语、痴呆、精神障碍、耳聋和运动不耐受，与典型的MELAS患者无明显差异[19]。但本组患者有显著的脑血管病危险因素，除糖尿病外，还可见高血压（3/10）及高脂血症（6/10），且颈动脉粥样硬化（6/7）及大脑中动脉狭窄（1/7）的比例也明显升高，这些因素都导致晚发型MELAS易被误诊为缺血性卒中。甚至有患者首先出现了缺血性卒中，而后才出现MELAS的脑卒中样发作，提示晚发型MELAS患者可以合并缺血性卒中。通过总结我们发现，详细的病史和家族史是明确诊断的第一步。本组9例携带m.3243A>G突变的患者有多年的糖尿病和（或）神经性耳聋病史，6例有母系遗传家族史，是提示MELAS诊断的重要线索。此外，虽然偏瘫是缺血性卒中的常见症状，但在本组患者中并不常见，仅2例在脑卒中样发作时出现偏瘫，比例较低。

脑卒中样发作的神经影像学特点也有助于诊断MELAS。本组晚发型患者的脑卒中样发作病灶主要分布在颞叶、枕叶和顶叶交界区，额叶和丘脑也可以被累及，与典型的MELAS患者无差异。上述病灶不符合血管分布，而且DWI上显示皮质高信号，提示细胞毒性水肿，而皮质下病灶无高信号，提示血管源性水肿，这些特点均与缺血性卒中不符。但值得注意的是，晚发型MELAS患者除上述典型MELAS皮质病变外，也可出现腔隙性缺血灶及梗死灶，主要分布在脑干、基底节区或放射冠区，为脑小血管病的常见受累部位，且这种改变并不少见[20]。

RRF是MELAS患者的典型病理改变，也是诊断MELAS的病理标准之一。但是，RRF并非见于所有的MELAS患者，仍有少部分患者骨骼肌病理无RRF。本研究行肌肉组织活检的8例患者中，有1例（例10）病理未见RRF。目前研究认为，RRF的形成

与肌纤维内突变型线粒体的比例、线粒体的增生程度及基因突变类型有关[21]。若肌纤维内突变型线粒体的比例较低或低龄时异常线粒体累积较少，可以无RRF出现，此后随着年龄的增长及异常线粒体的增多，才有RRF形成。此外，不同mtDNA突变出现RRFs的比例也有所不同。在携带编码还原型烟酰胺腺嘌呤二核苷酸（NADH）脱氢酶（ND）亚单位的mtDNA突变的患者中，RRF阴性的比例高于mtDNA的转运RNA（tDNA）编码基因突变[1,21]。而本组例10为*ND3*基因编码区m.10191T>C突变，推测是导致其RRF阴性的主要原因。

本组10例患者有9例携带m.3243A>G突变，提示m.3243A>G突变为晚发型MELAS的热点突变，与经典型患者相同[19]。回顾已报道的28例晚发型MELAS患者的基因检测结果，其中m.3243A>G突变24例，m.4332G>A、m.13513G>A、m.13635C>A和m.14487T>C突变各1例[3-16]，也支持这一结论。由此推测，共同的分子生物学基础是晚发型和经典型患者临床表型基本一致的原因。本组患者血液中m.3243A>G突变的比例较低，与文献中4%~31%的比例接近[3,5,12,14]，因此推测突变比例低可能是脑卒中样发作出现较晚的原因。有研究发现，当m.3243A>G突变的比例在10%~30%之间时，临床表型以糖尿病为主[22]，由此提示线粒体糖尿病患者随着年龄的增长，可能进展为MELAS。因此，早期识别这部分患者，及早给予左旋精氨酸、辅酶Q10以及左旋肉碱等药物治疗，可能延缓脑卒中样发作的发生。

利益冲突 无

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27th Congress of the European Society for Pediatric Neurosurgery

Time: May 3–6, 2020

Venue: Athens, Greece

Website: https://www.erasmus.gr/microsites/1179

The 27th Congress of the European Society for Pediatric Neurosurgery (ESPN) will take place in Athens, Greece on May 3–6, 2020. ESPN aims to organize an outstanding scientific and educational congress to facilitate the spread and exchange of knowledge, skills and attitudes, between experts, researchers, clinicians and trainees, and to continue the development of pediatric neurosurgery in Europe.

The ESPN Congress is organized on a biennial basis (traditionally in late April-early May) by the acting ESPN President in his country of origin. It is ESPN's main educational activity since its first organization in 1967 in Vienna, Austria, which constituted the Society's inaugural occasion. The Scientific Program is drafted by the ESPN Scientific Committee, in collaboration with the ESPN President. Plenary sessions host a series of invited lectures delivered by renowned experts in the field of Pediatric Neurosurgery and sister disciplines. Abstract submission on topics covering all major aspects of concurrent Pediatric Neurosurgery research and clinical practice lavishly provides for oral and poster presentations. Vibrant discussion is an integral part of all sessions, with the strategic positioning of Panel Tables on major issues addressed.

55th Annual Congress of Canadian Neurological Sciences Federation 2020

Time: June 7–10, 2020

Venue: Banff, Alberta, Canada

Website: http://congress.cnsfederation.org/

The 55th Canadian Neurological Sciences Federation (CNSF) Congress 2020 will take place in Banff, Alberta, Canada on June 7–10, 2020. This is a collegial meeting providing multidisciplinary courses relevant to all neuroscience specialties.

By the end of the Congress, delegates will be able to discuss advances in the management of acute and chronic neurological and neurosurgical disorders and their imaging appearances, discuss new findings in neurological and neurosurgical disorders and the role of neuroimaging in diagnosis and management, describe advances in neurological, neurosurgical and/or and neuroimaging care and techniques; and identify areas where there are gaps in learning (unperceived needs) not realized before attending the Congress and extend this professional learning after the Congress to the enhanced care of patients.