·神经肌肉病·

线粒体脑肌病伴高乳酸血症和卒中样发作患者头皮不同区域毛囊m.3243A>G突变率分析

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【摘要】 **目的** 比较线粒体脑肌病伴高乳酸血症和卒中样发作(MELAS)患者头皮不同区域毛囊线粒体DNA(mtDNA)突变率的差异,并探讨其与脑卒中样发作累及皮质病灶的关系。**方法** 采集7例MELAS患者8个头皮区域(双侧额叶、颞叶、顶叶、枕叶)毛囊DNA,聚合酶链反应-限制性片段长度多态性检测m.3243A>G突变率。**结果** 7例患者8个头皮区域毛囊m.3243A>G突变率为(60.57±7.71)%,左侧额叶、右侧额叶、左侧颞叶、右侧颞叶、左侧顶叶、右侧顶叶、左侧枕叶、右侧枕叶分别为(61.30±7.32)%、(65.41±5.85)%、(59.80±5.58)%、(57.59±14.47)%、(62.46±5.02)%、(60.11±7.11)%、(59.70±8.68)%、(59.42±6.28)%,各区域差异无统计学意义($F=0.537$,$P=0.802$)。脑卒中样发作病灶对应头皮区域与非病灶对应头皮区域毛囊m.3243A>G突变率差异亦无统计学意义[(60.33±8.70)%对(61.02±6.52)%;$t=0.319$,$P=0.751$]。**结论** 头皮毛囊是方便易取、无创性组织标本,可用于mtDNA突变检测。MELAS患者不同头皮区域毛囊mtDNA突变率无差异,脑卒中样发作病灶对应头皮区域与非病灶对应头皮区域毛囊mtDNA突变率亦无差异。

【关键词】 MELAS综合征; 毛囊; DNA,线粒体; 突变

The m.3243A > G mutation load in hair follicles from different scalp regions of patients with MELAS

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【**Abstract**】 **Objective** To investigate the mitochondrial DNA (mtDNA) mutation load in hair follicles from different scalp regions of patients with mitochondrial, encephalomyopathy with lactic acidosis and stroke-like episodes (MELAS), compare the mutation load in different scalp regions, and analyze the difference in mutation load between scalp regions with lesion site in the brain and scalp regions without lesion site in the brain. **Methods** Seven MELAS patients with m.3243A > G mutations were studied. Hair follicles were obtained from 8 scalp regions (bilateral frontal, temporal, parietal and occipital lobes) of all patients and DNA was extracted. Polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) was performed to detect the m.3243A > G mutation. **Results** The mean value of m.3243A > G mutation load in hair follicles from all patients was (60.57 ± 7.71)%. In different scalp regions, the mean mutation load was (61.30 ± 7.32)% in left frontal, (65.41 ± 5.85)% in right frontal, (59.80 ± 5.58)% in left temporal, (57.59 ± 14.47)% in right temporal, (62.46 ± 5.02)% in left parietal, (60.11 ± 7.11)% in right parietal, (59.70 ± 8.68)% in left occipital and (59.42 ± 6.28)% in right occipital regions, respectively. There was no significant difference in the m.3243A > G mutation load among different scalp regions ($F = 0.537$, $P = 0.802$). There was no significant difference in the mutation load between scalp regions corresponding lesion site of the brain and scalp regions incorresponding lesion site of the brain [(60.33 ± 8.70)% vs. (61.02 ± 6.52)%; $t = 0.319$, $P = 0.751$)]. **Conclusions** Hair follicles are convenient and noninvasive sampled tissue for detecting mtDNA mutations. There is no difference in the mutation load among different scalp regions.

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Furthermore, there is no difference between scalp regions corresponding lesion site of the brain and scalp regions incorresponding lesion site of the brain.

【Key words】 MELAS syndrome; Hair follicle; DNA, mitochondrial; Mutation

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线粒体脑肌病伴高乳酸血症和卒中样发作(MELAS)是最常见的线粒体病之一,约80%系线粒体DNA(mtDNA)tRNA$^{Leu(UUR)}$编码基因3243A>G突变所致[1-2]。脑卒中样发作是MELAS的主要临床表现,表现为癫痫发作、偏盲和偏瘫,常反复发作。病理学特征是大脑皮质板层样坏死,主要发生于大脑后部。头部MRI显示,大脑后部枕叶、颞叶或顶叶皮质病灶呈长T_2信号[3]。mtDNA突变是明确诊断MELAS的重要方法,可通过肌肉、外周血、尿液、唾液、头皮毛囊等不同组织细胞进行基因检测[4-6]。但不同组织mtDNA突变率存在较大差异,Kotsimbos等[4]和Ko等[7]认为,无创性组织标本中头皮毛囊mtDNA突变率最高,遂于1994年开始通过头皮毛囊提取DNA进行MELAS基因诊断。尽管20余年来,MELAS分子遗传学和分子发病机制研究取得较大进展[8-10],但其确切发病机制尚不清楚,目前主要有3种机制假说,即线粒体细胞病、线粒体血管病和非缺血性神经血管细胞学说[11],然而MELAS患者头部MRI显示脑卒中样发作病灶多见于大脑后部的原因尚不明确。由于mtDNA突变的异胞质性(heteroplasmy)在MELAS临床异质性中发挥一定作用[12-13],因此有理由推测,脑卒中样病灶神经元突变率可能更高。人类胚胎发育过程中,头皮毛囊、皮肤和神经系统均由外胚层分化,故我们提出假设,头皮毛囊mtDNA突变率与脑部病变存在一定关联性。鉴于此,本研究检测MELAS患者头皮毛囊mtDNA突变率,比较头皮不同区域毛囊mtDNA突变率的差异,并探讨其与脑卒中样发作累及皮质病灶的关系。

对象与方法

一、研究对象

研究对象均来自2015年12月-2017年12月在北京大学第一医院神经内科经骨骼肌病理学检查和基因检测诊断明确的MELAS患者,共7例,其中,男性2例,女性5例,均无血缘关系;年龄9~45岁,中位年龄17(12,33)岁;病程2个月至14年,中位病程3(2,10)年;7例(7/7)均有脑卒中样发作史,其中6例(6/7)出现智力减退,6例(6/7)癫痫发作,2例(2/7)精神障碍,1例(1/7)耳聋,6例(6/7)偏盲,2例(2/7)头痛,2例(2/7)言语模糊,2例(2/7)偏瘫;血浆乳酸3.00~4.30 mmol/L(0~2 mmol/L),中位值3.50(3.40,4.10)mmol/L;头部MRI显示,脑卒中样发作病灶位于枕叶6例(6/7)、顶叶6例(6/7)、颞叶5例(5/7)、额叶1例(1/7);脑电图均呈现异常;肌肉组织活检均存在破碎红纤维(RRF);基因检测均证实m.3243A>G突变(表1)。本研究经北京大学第一医院道德伦理委员会审核批准,所有患者或其家属均知情同意并签署知情同意书。

二、研究方法

1. 标本采集及玻璃奶法提取DNA 每例患者均采集8个头皮区域(双侧额叶、颞叶、顶叶、枕叶)毛囊,每一区域采集2~3个毛囊,置于1.50 μl EP管中,加入2~3 μl玻璃奶和100 μl溶胶结合液,研磨棒仔细研磨,55 ℃孵育5 min,每分钟摇晃1次;于离心半径10 cm、12 000 r/min离心30 s,弃上清液,加入300 μl体积分数为70%的乙醇溶液,混匀,于离心半径10 cm、12 000 r/min离心30 s,弃上清液,重复3次,于离心半径10 cm、12 000 r/min离心30 s,弃上清液,55 ℃沉淀静置至干透;加入10 μl TE缓冲液,混合均匀,于离心半径10 cm、12 000 r/min离心1 min,取上清液,于4或-20 ℃保存备用。

2. 聚合酶链反应-限制性片段长度多态性检测 (1)DNA片段扩增:采用聚合酶链反应(PCR)扩增DNA片段,正向引物序列为5'-GGACAAGAGAAATAAGGCC-3'(mtDNA位置:m.3130-3149),反向引物序列为5'-AACGTTGGGGCCTTTGCGTA-3'(mtDNA位置:m.3423-3404)。PCR反应体系共25 μl,包含1 U Taq酶,1 μl头皮毛囊DNA,上下游引物各5 pmol/L,

表1 7例MELAS患者的临床资料

Table 1. Clinical features of 7 MELAS patients

Case	Sex	Age (year)	Symptom	Plasma lactate (mmol/L)	Stroke-like lesions on MRI	Muscle biopsy	Gene mutation
1	Male	17	Deafness, seizures, psychological symptoms, recognition decline	3.40	Right parietal lobe	RRF	m.3243A > G
2	Female	19	Seizures, hemianopsia, psychological symptoms, recognition decline	4.30	Left temporo-parieto-occipital lobe, right occipital lobe	RRF	m.3243A > G
3	Female	33	Seizures, recognition decline, hemianopsia, slurring of speech	3.50	Left temporo-occipital lobe, right temporal lobe	RRF	m.3243A > G
4	Female	9	Recognition decline, seizures, hemianopsia, headache	3.70	Bilateral temporo-parieto-occipital lobes	RRF	m.3243A > G
5	Male	45	Slurring of speech, hemianopsia, hemiparesis	4.10	Left temporo-parieto-occipital lobe	RRF	m.3243A > G
6	Female	12	Seizures, recognition decline, hemianopsia, hemiparesis	3.00	Right parieto-occipital lobe	RRF	m.3243A > G
7	Female	13	Headache, seizures, recognition decline, hemianopsia	3.50	Bilateral fronto-parieto-occipital lobes, right temporal lobe	RRF	m.3243A > G

RRF, ragged red fiber, 破碎红纤维

表2 7例MELAS患者8个头皮区域毛囊m.3243A > G突变率(%)

Table 2. The m.3243A > G mutation load in hair follicles from different scalp regions of 7 patients with MELAS (%)

Case	Left frontal lobe	Right frontal lobe	Left temporal lobe	Right temporal lobe	Left parietal lobe	Right parietal lobe	Left occipital lobe	Right occipital lobe
1	56.39	66.72	62.28	57.87	55.76	53.49*	49.21	50.83
2	—	57.11	61.34*	28.94	—*	60.36	62.04*	54.82*
3	52.68	59.55	47.49*	60.65*	57.86	56.71	45.74*	57.76
4	57.94	71.37	59.65*	64.51*	61.35*	62.81*	61.52*	61.07*
5	67.97	66.95	62.18*	66.19	68.49*	70.87	65.54*	59.04
6	71.94	—	63.98	67.36	66.67	65.96	67.21	70.89*
7	60.85*	70.75*	61.66	—*	64.62*	50.55	66.62*	61.49*

*scalp regions corresponding lesion site of the brain, 脑卒中样发作病灶对应头皮区域; —, not available, 无数据

脱氧核糖核苷三磷酸(dNTP)100 μmol/L, Tris缓冲液10 mmol/L, 氯化钾溶液10 mmol/L, 镁离子溶液1.50 mmol/L。PCR反应条件为:94 ℃ 5 min、94 ℃ 30 s、58 ℃ 30 s、72 ℃ 30 s, 重复35次, 最后72 ℃延伸7 min。DNA扩增片段长度为294 bp。(2)DNA酶切与突变率计算:PCR扩增产物以ApaⅠ限制性内切酶于25 ℃水浴中酶切2 h, 酶切产物进行琼脂糖凝胶电泳1 h, 在凝胶成像仪上于紫外分光光度计302 nm波长处计数电泳条带, 野生型mtDNA仅可见1条电泳条带(294 bp)、m.3243A > G突变酶切为2条电泳条带(178和116 bp), 并计算m.3243A > G突变率, 突变率(%) = 突变型电泳条带密度/(突变型电泳条带密度 + 野生型电泳条带密度) × 100%。

3. 统计分析方法 采用SPSS 17.0统计软件进行数据处理与分析。呈正态分布的计量资料以均数 ± 标准差($\bar{x} \pm s$)表示, 8个头皮区域毛囊m.3243A > G突变率的比较采用单因素方差分析;脑卒中样发作病灶对应头皮区域与非病灶对应头皮区域毛囊m.3243A > G突变率的比较采用两独立样本的t检验。以$P \leq 0.05$为差异具有统计学意义。

结 果

本组7例患者8个头皮区域毛囊均检测到m.3243A > G突变(表2), m.3243A > G突变率为28.94% ~ 71.94%、平均(60.57 ± 7.71)%, 其中, 左侧额叶毛囊52.68% ~ 71.94%、平均(61.30 ± 7.32)%, 右侧额叶毛囊57.11% ~ 71.37%、平均(65.41 ± 5.85)%, 左侧颞叶毛囊47.49% ~ 63.98%、平均(59.80 ± 5.58)%, 右侧颞叶毛囊28.94% ~ 67.36%、平均(57.59 ± 14.47)%, 左侧顶叶毛囊55.76% ~ 68.49%、平均(62.46 ± 5.02)%, 右侧顶叶毛囊50.55% ~ 70.87%、平均(60.11 ± 7.11)%, 左侧枕叶毛囊45.74% ~ 67.21%、平均(59.70 ± 8.68)%, 右侧枕叶毛囊50.83% ~ 70.89%、平均(59.42 ± 6.28)%, 8个头皮区域毛囊m.3243A > G突变率差异无统计学意义($F = 0.537$, $P = 0.802$)。脑卒中样发作病灶对应头皮区域毛囊m.3243A > G突变率为45.74% ~ 70.89%、平均(60.33 ± 8.70)%, 非病灶对应头皮区域

毛囊m.3243A > G突变率为28.94%～71.94%、平均(61.02 ± 6.52)%，二者差异无统计学意义(t = 0.319，P = 0.751)。

讨　论

临床用于mtDNA突变检测的组织包括肌肉、外周血、尿液、唾液和头皮毛囊等[14]，研究显示，肌肉组织mtDNA突变率最高，但肌肉组织检查为有创性操作[6,15]。Chinnery等[15]认为，在无创性组织标本中头皮毛囊mtDNA突变率最高，其次是口腔黏膜，最低的是外周血。Ma等[5]的研究显示，尿液m.3243A > G突变率(62%)显著高于外周血(36%)，而头皮毛囊与唾液mtDNA突变率无显著差异。Chiang等[16]检测1例MELAS患者不同组织m.3243A > G突变率，结果显示，白细胞为56%、头皮毛囊为70%、口腔黏膜为64%。本研究7例MELAS患者8个头皮区域毛囊m.3243A > G突变阳性率为(60.57 ± 7.71)%，与既往研究相近[5,15-16]，证实头皮毛囊用于MELAS基因检查具有较高的稳定性。

头皮毛囊还可以用于其他类型的mtDNA突变检测，如m.8344A > G或m.8993T > G/C突变[4,17]。但Mkaouar-Rebai等[18]在m.9478T > C突变导致的Leigh综合征患者头皮毛囊中未检测到该突变。因此，不同类型mtDNA突变在头皮毛囊中存在较大差异，头皮毛囊mtDNA突变阴性不能完全排除线粒体病，还应结合其他组织进行基因检测。

多项研究显示，MELAS患者脑组织损害以大脑后部皮质为主[1,3,19]，本研究头部MRI所见也符合这一规律，除1例患者同时出现额叶病灶外，余6例脑卒中样发作病灶均位于枕叶、顶叶或颞叶。迄今MELAS选择性累及大脑后部的机制尚不明确。为探讨MELAS患者mtDNA突变率与不同脑区病理改变的相关性，Betts等[20]对2例存在m.3243A > G突变的MELAS患者进行尸体解剖，结果显示，m.3243A > G突变率与脑组织病理改变程度之间无关联性。由于毛发和神经系统均由外胚层分化而来，故推测头皮毛囊mtDNA突变率可能反映脑组织突变率[20]，同时，Enns等[21]发现，即使是同一例患者，不同头皮区域毛囊m.8993T > G突变率亦不同，因此，本研究检测8个头皮区域毛囊m.3243A > G突变率，且各区域毛囊m.3243A > G突变率差异无统计学意义，脑卒中样发作病灶对应头皮区域与非病灶对应头皮区域毛囊m.3243A > G突变率差异亦无统计学意义，与Betts等[20]的结果相一致，提示m.3243A > G的突变率可能并非MELAS患者脑卒中样发作部位的主要决定因素。Betts等[20]发现，软脑膜血管壁和各脑区皮质血管细胞色素C氧化酶(COX)活性下降程度最为显著，其mtDNA突变率亦最高，推测血管线粒体功能障碍是MELAS的主要发生机制。此外，Iizuka和Sakai[11]认为，MELAS患者病灶集中于大脑后部的特点可能与枕叶皮质神经元突触密度较高且易兴奋有关，这些区域对能量的需求高于其他脑区，供需矛盾更加突出，更易导致枕叶出现脑卒中样发作病灶。

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·小词典·

中英文对照名词词汇(三)

接触蛋白相关蛋白-2 contactin-associated protein 2(Caspr2)
结核分枝杆菌 Mycobacterium tuberculosis(MTB)
结核性脑膜炎 tuberculous meningitis(TBM)
进行性肌营养不良症 progressive muscular dystrophy(PMD)
静脉注射免疫球蛋白 intravenous immunoglobulin(IVIg)
巨细胞病毒 cytomegalovirus(CMV)
聚合酶链反应-限制性片段长度多态性 polymerase chain reaction-restriction fragment length polymorphism(PCR-RFLP)
聚偏二氟乙烯 polyvinylidene fluoride(PVDF)
均数差 mean difference(MD)
Leiden开放基因变异数据库 Leiden Open Variation Database(LOVD)
抗核抗体 anti-nuclear antibody(ANA)
抗逆转录病毒疗法 antiretroviral therapy(ART)
肯尼迪病 Kennedy´s disease(KD)
快速傅里叶变换 fast Fourier transform(FFT)
扩散加权成像 diffusion-weighted imaging(DWI)
扩散张量成像 diffusion tensor imaging(DTI)
Newcastle-Ottawa量表 Newcastle-Ottawa Scale(NOS)
磷脂酰肌醇3,5-二磷酸 phosphatidylinositol 3, 5-bisphosphate [PI (3, 5) P2]
颅脑创伤 traumatic brain injury(TBI)
路易小体 Lewy body(LB)
卵巢性脑白质营养不良 ovarioleukodystrophies disease(OLD)
卵泡刺激素 follicle stimulating hormone(FSH)
美国国立综合癌症网 National Comprehensive Cancer Network(NCCN)
美国食品与药品管理局 Food and Drug Administration(FDA)
美国医学遗传学和基因组学会 American College of Medical Genetics and Genomics (ACMG)
梅毒螺旋体 Treponema pallidum(TP)
面-肩-肱型肌营养不良症 facioscapulohumeral muscular dystrophy(FSHD)
脑深部电刺激术 deep brain stimulation(DBS)
脑小血管病 cerebral small vessel disease(cSVD)
内-中膜厚度 intima-media thickness(IMT)
鸟苷二磷酸 guanosine diphosphate (GDP)
鸟苷三磷酸 guanosine triphosphate(GTP)
欧洲药物管理局 European Medicines Agency(EMA)
帕金森病 Parkinson´s disease(PD)
疲劳严重程度评分 Fatigue Severity Score(FSS)
匹兹堡睡眠质量指数 Pittsburgh Sleep Quality Index(PSQI)
平山病 Hirayama´s disease(HD)
破碎红纤维 ragged red fiber(RRF)
前信使RNA premessenger RNA(pre-mRNA)