

# 维生素 B<sub>12</sub> 依赖型甲基丙二酸血症一家系临床表型和基因突变分析及疗效评价

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**【摘要】** **目的** 探讨维生素 B<sub>12</sub> 依赖型甲基丙二酸血症家系临床特点、基因突变和维生素 B<sub>12</sub> 治疗效果。**方法** 采集一维生素 B<sub>12</sub> 依赖型甲基丙二酸血症家系共 4 名成员临床资料, 抽取外周静脉血行血浆氨基酸和酰基肉碱谱分析及基因检测, 评价维生素 B<sub>12</sub> 治疗效果。**结果** 家系中先证者 12 岁发病, 以学习成绩下降、性格改变为首发症状, 病程中出现幻觉、双下肢无力; 先证者之弟主要表现为易怒、学习成绩较差。经血浆氨基酸和酰基肉碱谱分析, 先证者及其弟血浆丙酰肉碱、丙酰肉碱/乙酰肉碱比值升高, 尿液甲基丙二酸水平升高。基因检测显示, 先证者及其弟均存在 *MMACHC* 基因复合杂合突变 c.482G > A (p.Arg161Gln) 和 c.609G > A (p.Trp203X), 其父携带 *MMACHC* 基因错义突变 c.482G > A (p.Arg161Gln), 其母携带 *MMACHC* 基因无义突变 c.609G > A (p.Trp203X)。经维生素 B<sub>12</sub> 治疗后均症状好转。**结论** 晚发型维生素 B<sub>12</sub> 依赖型甲基丙二酸血症系 *MMACHC* 基因复合杂合突变所致, 维生素 B<sub>12</sub> 治疗反应良好, 早期诊断、及时治疗对患者预后意义重大。

**【关键词】** 甲基丙二酸; 代谢缺陷, 先天性; 维生素 B<sub>12</sub>; 表型; 基因; 突变; 系谱

## Analysis of clinical phenotype and genetic mutation with outcome evaluation in one family of vitamin B<sub>12</sub>-dependent methylmalonic aciduria

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**【Abstract】** **Objective** To explore the clinical features, genetic mutation and vitamin B<sub>12</sub> therapeutic effectiveness in vitamin B<sub>12</sub>-dependent methylmalonic acidemia (MMA). **Methods** Clinical data in a pedigree of 4 members with vitamin B<sub>12</sub>-dependent MMA was collected. Peripheral blood samples were collected for plasma amino acids and acylcarnitines and gene mutation analysis. The therapeutic efficacy of vitamin B<sub>12</sub> was evaluated. **Results** The initial presentations of the proband were underachievement and personality changes in 12-year old, and accompanied by visual hallucinations and weakness of lower limbs during the course of disease. The younger brother of the proband presented with bad-temper and lower achievement. The analysis of plasma amino acid and acylcarnitine showed that proband and his younger brother's plasma propionylcarnitine and propionylcarnitine/acetylcarnitine ratio, and the level of methylmalonic acid in urine were increased significantly. Compound heterozygous mutation of c.482G > A (p.Arg161Gln) and c.609G > A (p.Trp203X) in *MMACHC* gene were seen in the proband and her younger brother. Her father carried *MMACHC* gene missense mutation c.482G > A (p.

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Arg161Gln), while her mother carried *MMACHC* gene nonsense mutation c.609G > A (p.Trp203X). Symptoms of the proband were improved after vitamin B<sub>12</sub> therapy. **Conclusions** The late-onset vitamin B<sub>12</sub>-dependent MMA is caused by compound heterozygote mutation of *MMACHC* gene. It had good responsive to vitamin B<sub>12</sub> therapy. Early diagnosis and timely treatment may play a critical role for the outcomes of patients with this disease.

**【Key words】** Methylmalonic acid; Metabolism, inborn errors; Vitamin B<sub>12</sub>; Phenotype; Genes; Mutation; Pedigree

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甲基丙二酸血症(MMA)cblC型系*MMACHC*基因突变导致其编码的cblC蛋白缺乏,使L-甲基丙二酸无法转变为琥珀酸而在血液中蓄积,是临床最常见的维生素B<sub>12</sub>代谢障碍性疾病,呈常染色体隐性遗传,发病率为1/10万~1/6万<sup>[1]</sup>。根据发病年龄,可以分为早发型(1岁内发病)和晚发型甲基丙二酸血症。迄今文献报道仅约10%患者为晚发型甲基丙二酸血症<sup>[2-3]</sup>。维生素B<sub>12</sub>依赖型甲基丙二酸血症临床罕见,通常于儿童期、青少年期或成年期发病,主要表现为精神症状、意识障碍和神经系统症状等,经及时治疗预后较好<sup>[4-5]</sup>,属可治性神经系统遗传性疾病。本研究报道一晚发型甲基丙二酸血症家系,总结其临床表现、血液化学、基因检测和维生素B<sub>12</sub>治疗后转归,探讨维生素B<sub>12</sub>治疗MMAcblC型的作用机制,以期提高儿科和神经科医师对甲基丙二酸血症的认识。

## 对象与方法

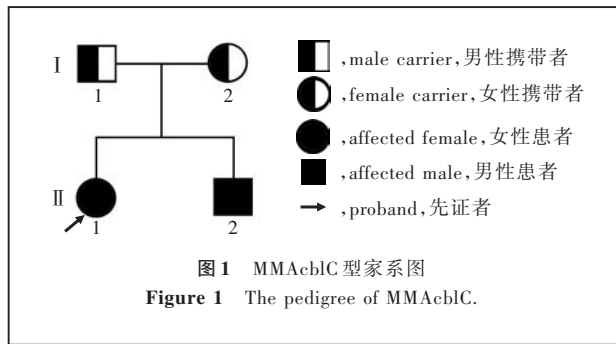
### 一、研究对象

本研究MMAcblC型患者于中山大学附属第一医院神经科就诊,其家系2代共4名成员(图1),汉族,其中2例符合常染色体隐性遗传特点。

先证者 女性,13岁,主因性格改变1年、双下肢无力2个月,于2016年11月24日至我院神经科门诊就诊。患者1年前无明显诱因出现易激惹、易哭闹,学习成绩下降,未予重视;2个月前出现双下肢无力,勉强能够独立行走,上楼梯费力,无肢体麻木,双上肢未见异常;1月余前出现幻觉,以幻视为主,逐渐进展至行走不能。1个月前曾至外院就诊,诊断为“可疑线粒体脑肌病或脑炎”,予静脉注射免

疫球蛋白(IVIg)和甲泼尼龙等治疗(具体剂量不详),症状无明显好转,为求进一步诊断与治疗,遂至我院就诊。患儿足月顺产,单胎,生长发育和智力发育正常;父母身体健康,无相似临床症状,否认近亲婚配。门诊体格检查:身高和体重于同龄儿童正常范围。神经系统检查:高级智能和脑神经检查未见异常,双侧小腿肌萎缩,双下肢近端肌力3级、远端4级,肌张力降低,双上肢肌力5级,肌张力正常;双下肢痛触觉和关节位置觉减退,四肢腱反射未引出,双下肢Babinski征阳性,脑膜刺激征阴性。实验室检查:血尿便常规、肝肾功能试验、血液化学、免疫学指标、血氨、血清维生素B<sub>12</sub>均于正常值范围,血清同型半胱氨酸(Hcy)165.30 μmol/L(5~20 μmol/L)。影像学检查:胸部X线未见明显异常。头部MRI显示轻度脑萎缩,尤以白质显著,双侧侧脑室旁长T<sub>1</sub>、长T<sub>2</sub>信号,扩散加权成像(DWI)呈颞顶叶放射冠低信号,表观扩散系数(ADC)升高(图2)。磁共振波谱(MRS)显示,N-乙酰天冬氨酸(NAA)峰、肌酸(Cr)峰、胆碱(Cho)峰峰值降低(图3)。电生理学检查:心电图未见明显异常。脑电图显示中度异常,以θ波为主要背景波。

患儿Ⅱ2 男性,10岁,先证者之弟,于2016年12月6日至我院神经科门诊就诊。患儿足月顺产,单胎,18个月方可独立行走和会说话,智力发育较同龄正常儿童差,目前读小学,学习成绩较差,易怒,未予重视。门诊体格检查:身高和体重于同龄儿童正常范围。神经系统检查:注意力和计算力较差,语言复述能力较差,脑神经检查未见明显异常;四肢肌力5级、肌张力正常,感觉系统未见异常,腱反射降低,病理反射未引出,脑膜刺激征阴性。实



实验室检查:血尿便常规、肝肾功能试验均于正常值范围,血氨  $51 \mu\text{mol/L}$  ( $10 \sim 47 \mu\text{mol/L}$ ),血清维生素  $\text{B}_{12}$  于正常值范围,血清同型半胱氨酸  $84.20 \mu\text{mol/L}$ 。

## 二、研究方法

1. 血浆氨基酸和酰基肉碱谱分析 采集先证者及其弟外周静脉血各 2 ml 制备干血滤纸,API3200 液质联用仪(美国 SCIEX 公司)采用串联质谱法行血浆氨基酸和酰基肉碱谱分析。采集先证者及其弟尿液制备 3 张尿液滤纸片,7890/5975C 气相质谱联用仪(美国 Agilent 公司)行尿液气相色谱质谱分析,检测尿液各种有机酸之间的比值。

2. 目标区域捕获测序与数据分析 经先证者父母同意,采集该家系 4 名成员外周静脉血各 2 ml,行甲基丙二酸血症相关二代基因测序(NGS)。(1)基因组 DNA 提取和基因组文库制备:2 ml 外周静脉血置于乙二胺四乙酸(EDTA)抗凝管中,采用 QIAmp DNA Mini Kit 试剂盒(德国 QIAGEN 公司)提取基因组 DNA。取  $3 \mu\text{g}$  DNA,以 Tris-乙二胺四乙酸(EDTA)缓冲液稀释至  $30 \text{ ng}/\mu\text{l}$ ,采用 Covris-S220 超声仪(美国 Covaris 公司)将样本 DNA 片段化为长度 150 bp,采用标准 DNA 文库构建试剂盒(北京迈基诺基因科技股份有限公司)进行片段末端修复加“腺嘌呤”和产物纯化,经聚合酶链反应(PCR)扩增后,采用 Nanodrop 2000 紫外分光光度计(美国 Thermo 公司)进行 DNA 文库定量。(2)目标区域捕获测序:采用 GenCap 液相捕获目标基因技术对已知的 176 种代谢性疾病相关基因进行探针捕获,覆盖每种基因的外显子及其上下游内含子长度 50 bp 区域,生物素标记的探针与文库 DNA 杂交,链霉素标记的磁珠共价结合生物素标记的探针,抓取目的基因,磁力架吸附携带目的基因的磁珠,洗脱纯化,富集目的基因,再采用 NextSeq 500 高通量测序仪(美国 Illumina 公司)进行双端测序。(3)数据处理与分析:原始数据剔除接头和低质量短序列( $< 40 \text{ bp}$ ),

BWA 软件(<http://bio-bwa.sourceforge.net/>)将预处理的数据与 hg19 人类基因组数据库(<http://hgdownload.cse.ucsc.edu/>)进行比对,GATK3.3.0 软件包(<https://www.broadinstitute.org/gatk>)校准并重新匹配至参考序列,单碱基突变采用 GATK UnifiedGenotyper 分析,单核苷酸多态性(SNP)和插入/缺失突变采用共识编码序列数据库(CCDS)、hg19 人基因组数据库、单核苷酸多态性数据库信息进行注释,确定候选变异位点,SIFT 预测软件(<http://sift.jcvi.org>)对变异位点进行生物信息学分析。

3. Sanger 测序验证 据基因变异位点设计上下游引物,由赛默飞世尔科技(中国)有限公司合成,上游引物序列:5'-CCTCCATGACCTTGCTTTTC-3',下游引物序列:5'-GGGATGCAGGTGGTGAGAC-3'。PCR 反应体系共  $25 \mu\text{l}$ ,反应条件为  $95 \text{ }^\circ\text{C}$  10 min;  $94 \text{ }^\circ\text{C}$  30 s、 $64 \text{ }^\circ\text{C}$  30 s、 $72 \text{ }^\circ\text{C}$  45 s,共 3 个循环;  $94 \text{ }^\circ\text{C}$  30 s、 $62 \text{ }^\circ\text{C}$  30 s、 $72 \text{ }^\circ\text{C}$  45 s,共 5 个循环;  $94 \text{ }^\circ\text{C}$  30 s、 $60 \text{ }^\circ\text{C}$  30s、 $72 \text{ }^\circ\text{C}$  45s,共 10 个循环;  $94 \text{ }^\circ\text{C}$  30 s、 $58 \text{ }^\circ\text{C}$  30 s、 $72 \text{ }^\circ\text{C}$  45 s,共 17 个循环;最终  $72 \text{ }^\circ\text{C}$  5 min;  $4 \text{ }^\circ\text{C}$  冷却备用。然后采用 ABI3130xl 测序仪[赛默飞世尔科技(中国)有限公司]将 PCR 扩增产物进行毛细管电泳,测序结果与标准参考序列(NM\_001330540.1)进行比对。

## 结 果

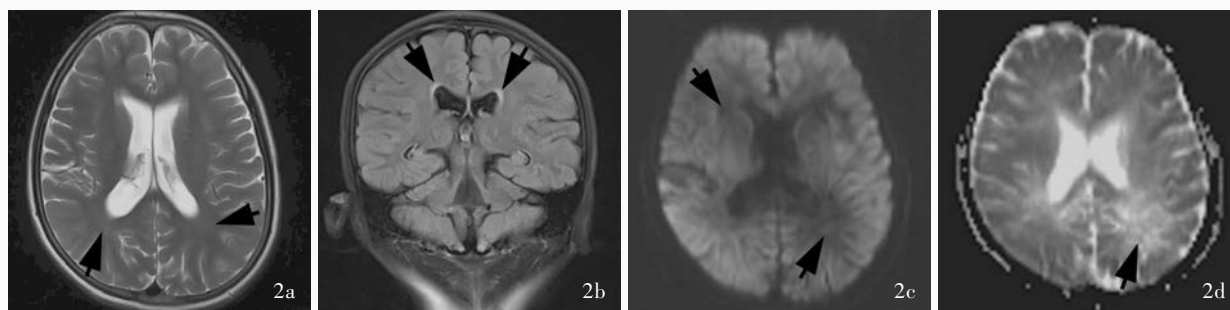
### 一、临床特征

该家系共 2 代 4 名成员,男性 2 名,女性 2 名;先证者 12 岁发病,主要表现为性格改变、学习成绩下降,病程中出现幻觉、双下肢无力症状,病程 1 年;先证者之弟自幼表现为易怒、智力低下,未明显累及运动系统。

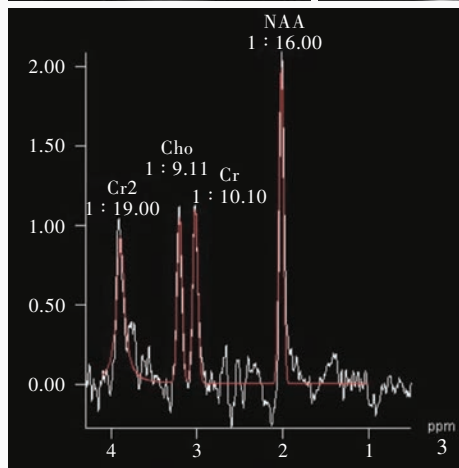
### 二、血浆氨基酸和酰基肉碱谱分析

先证者血浆甲硫氨酸为  $7.80 \mu\text{mol/L}$  ( $8.50 \sim 50.00 \mu\text{mol/L}$ ),丙二酸  $0.60 \mu\text{mol/L}$  ( $0 \sim 0.30 \mu\text{mol/L}$ ),丙酰肉碱(C3)  $6.39 \mu\text{mol/L}$  ( $0.30 \sim 5.00 \mu\text{mol/L}$ ),丙酰肉碱/乙酰肉碱(C2)比值为 0.41 ( $0.02 \sim 0.25$ );尿液甲基丙二酸水平为  $63.70 \mu\text{mol/L}$  ( $0 \sim 4 \mu\text{mol/L}$ )。先证者之弟血浆丙酰肉碱  $5.29 \mu\text{mol/L}$ , C3/C2 比值为 0.59,天冬氨酸为  $62.60 \mu\text{mol/L}$  ( $18 \sim 47 \mu\text{mol/L}$ ),精氨酸  $95.50 \mu\text{mol/L}$  ( $11 \sim 69 \mu\text{mol/L}$ ),丙氨酸  $576.70 \mu\text{mol/L}$  ( $210 \sim 545 \mu\text{mol/L}$ ),谷氨酰胺水平为  $702 \mu\text{mol/L}$  ( $249 \sim 579 \mu\text{mol/L}$ );尿液甲基丙二酸为  $75 \mu\text{mol/L}$ 。





**图 2** 头部 MRI 检查所见 2a 横断面 T<sub>2</sub>WI 显示,轻度脑萎缩,尤以白质显著(箭头所示),双侧侧脑室轻度扩大 2b 冠状位 FLAIR 成像显示,双侧侧脑室旁异常高信号(箭头所示) 2c 横断面 DWI 显示,双侧颞枕叶深部侧脑室旁异常低信号(箭头所示) 2d 横断面 ADC 图显示病变呈高信号(箭头所示) **图 3** 头部 MRS 显示,左侧侧脑室旁 NAA 峰、Cr 峰、Cho 峰和 NAA/(Cho + Cr) 比值降低,考虑白质髓鞘化不良,提示代谢性疾病



**Figure 2** Head MRI findings Axial T<sub>2</sub>WI showed mild encephalatrophy, especially in the white matter (arrows indicate), and slight enlargement of the bilateral ventricles (Panel 2a). Coronal FLAIR image showed abnormal hyperintense signals in bilateral periventricular area (arrows indicate, Panel 2b). Axial DWI showed abnormal hypointense signal in the deep part of bilateral temporo-occipital lobe beside lateral ventricle (arrows indicate, Panel 2c). Axial ADC showed hyperintensities in the lesion (arrow indicates, Panel 2d). **Figure 3** MRS showed decrease of NAA, Cr, Cho and NAA/(Cho + Cr) in left periventricular regions, which reflected of neuronal damage and malformation in white matter myelination and suggested metabolic disease.

### 三、基因检测

先证者存在 *MMACHC* 基因复合杂合突变,包括错义突变 c.482G > A (p.Arg161Gln) 和无义突变 c.609G > A (p.Trp203X),符合 MMAcblC 型的诊断(图 4a)。先证者之弟亦存在 *MMACHC* 基因复合杂合突变,包括错义突变 c.482G > A (p.Arg161Gln) 和无义突变 c.609G > A (p.Trp203X,图 4b)。进一步对其父母行 *MMACHC* 基因检测,提示错义突变 c.482G > A (p.Arg161Gln) 源自其父(图 4c)、无义突变 c.609G > A (p.Trp203X) 源自其母(图 4d)。2 例患者最终明确诊断为 MMAcblC 型合并高同型半胱氨酸血症。

### 四、治疗

先证者明确诊断后即予甲钴胺 1 mg/d 肌肉注射,左卡尼汀 2 g/d 静脉滴注,以及利培酮 0.50 g/次、2 次/d 口服控制幻视,共住院 13 d,出院时幻视消失,双下肢肌力 4 级、肌张力降低,搀扶可行走。出院后予以甲钴胺 1 mg/次、3 次/d 和左卡尼汀 1 g/次、2 次/d 口服,并嘱低蛋白饮食。出院后 3 个月门诊随访,临床症状好转,双下肢肌力 5 级,可独立行走,未再出现幻觉,复查血浆氨基酸和酰基肉碱谱分析,丙酰肉碱降至正常值范围,C3/C2 比值 0.27。先

证者之弟明确诊断后予甲钴胺 1 mg/次、3 次/d 和左卡尼汀 1 g/次、2 次/d 口服,嘱低蛋白饮食。3 个月后门诊随访,语言复述能力较前好转,注意力和计算力欠佳。

### 讨 论

甲基丙二酸血症是维生素 B<sub>12</sub> 代谢障碍性疾病,可以根据维生素 B<sub>12</sub> 在细胞内代谢障碍累及环节分型(图 5<sup>[4]</sup>,表 1)。人体从食物中摄取的游离维生素 B<sub>12</sub> 在体内与内因子结合形成稳定复合物,在回肠远端与肠黏膜细胞膜受体结合(维生素 B<sub>12</sub> 转运蛋白复合物)而被吸收。维生素 B<sub>12</sub> 进入细胞后自其转运蛋白复合物释放至细胞质内,在 cblC 蛋白催化下形成 Co(II)cbl 蛋白(即带 2 价电子的氧化态 cbl 蛋白),一部分转运至线粒体内转化为腺苷钴胺素(AdoCbl),参与线粒体内支链氨基酸和奇数链脂肪酸代谢,人体必需的支链氨基酸和奇数链脂肪酸在分解代谢过程中生成甲基丙二酸,在甲基丙二酰辅酶 A 变位酶(MUT)和 AdoCbl 共同催化下生成琥珀酰辅酶 A,参与三羧酸循环,若 MUT 或 AdoCbl 代谢异常,可以导致甲基丙二酸、丙酸等中间代谢产物堆积,引起单纯型甲基丙二酸血症,包括 cblA 型、

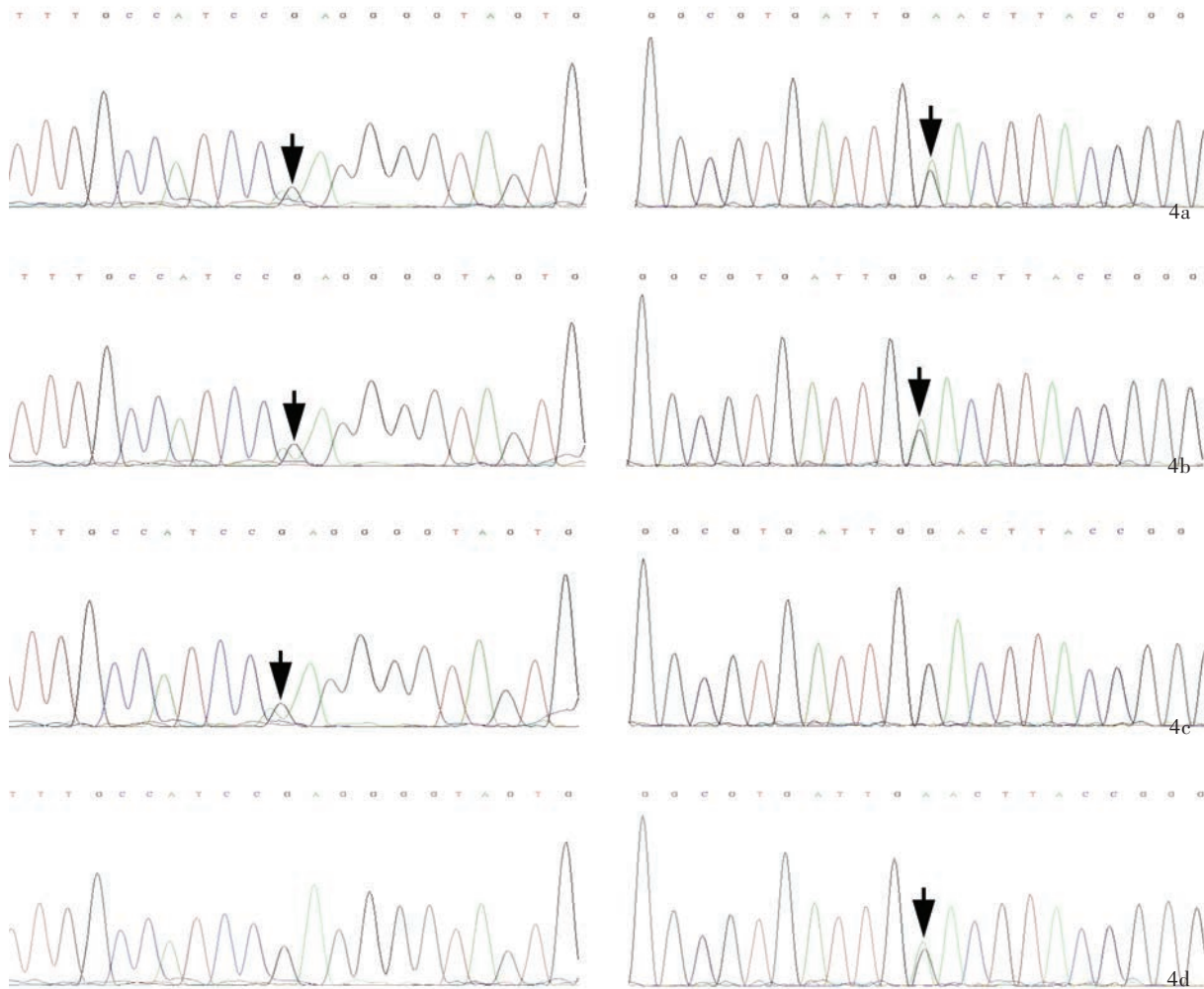


图4 *MMACHC* 基因检测所见 4a 先证者存在 *MMACHC* 基因复合杂合突变,包括错义突变 c.482G>A (p.Arg161Gln, 箭头所示, 左图) 以及无义突变 c.609G>A (p.Trp203X, 箭头所示, 右图) 4b 先证者之弟存在 *MMACHC* 基因复合杂合突变,包括错义突变 c.482G>A (p.Arg161Gln, 箭头所示, 左图) 以及无义突变 c.609G>A (p.Trp203X, 箭头所示, 右图) 4c 先证者之父亲存在 *MMACHC* 基因错义突变 c.482G>A (p.Arg161Gln, 箭头所示) 4d 先证者之母存在 *MMACHC* 基因无义突变 c.609G>A (p.Trp203X, 箭头所示)

Figure 4 Analysis of *MMACHC* gene test Proband had compound heterozygous mutation in *MMACHC* gene, including missense mutation c.482G>A (p.Arg161Gln, arrow indicates, left panel) and nonsense mutation c.609G>A (p.Trp203X, arrow indicates, right panel, Panel 4a). Proband's younger brother had the same compound heterozygous mutation as the proband (arrows indicate, Panel 4b). The proband's father carried *MMACHC* gene missense mutation c.482G>A (p.Arg161Gln, arrow indicates, Panel 4c). The proband's mother carried *MMACHC* gene nonsense mutation c.609G>A (p.Trp203X, arrow indicates, Panel 4d).

cb1B型和mut型3种亚型;另一部分在细胞质内转化为甲钴胺(MeCbl),参与催化同型半胱氨酸转化为甲硫氨酸<sup>[4]</sup>,若同时出现AdoCbl和MeCbl合成不足,可以影响同型半胱氨酸和甲基丙二酸的代谢,使甲基丙二酸和同型半胱氨酸蓄积<sup>[1]</sup>,导致甲基丙二酸血症合并高同型半胱氨酸血症,包括cb1C型、cb1D型、cb1F型和cb1J型<sup>[6-7]</sup>,尤以cb1C型常见<sup>[2,8]</sup>。

大多数甲基丙二酸血症为早发型,1岁内发病,表现为喂养困难、生长发育迟滞、癫痫发作、肌张力降低、酮症酸中毒等,除神经系统症状外,还有肝肾

功能障碍表现等,若无早期干预,病死率较高<sup>[9-10]</sup>,因此,国外和国内部分地区已将甲基丙二酸血症作为新生儿出生缺陷的常规筛查项目<sup>[8,11]</sup>。晚发型甲基丙二酸血症患者少见,临床表现多样,既往有文献报道,1岁至学龄期前发病的患儿以溶血性尿毒综合征(HUS)和肺动脉高压为主要表现,而青少年期或成年期发病的患者则以不典型神经精神症状为主要表现或仅表现为学习困难、情绪障碍等,还可合并共济失调、厌食、癫痫发作等,临床明确诊断困难,常延误治疗<sup>[12-13]</sup>。本研究家系中先证者以学

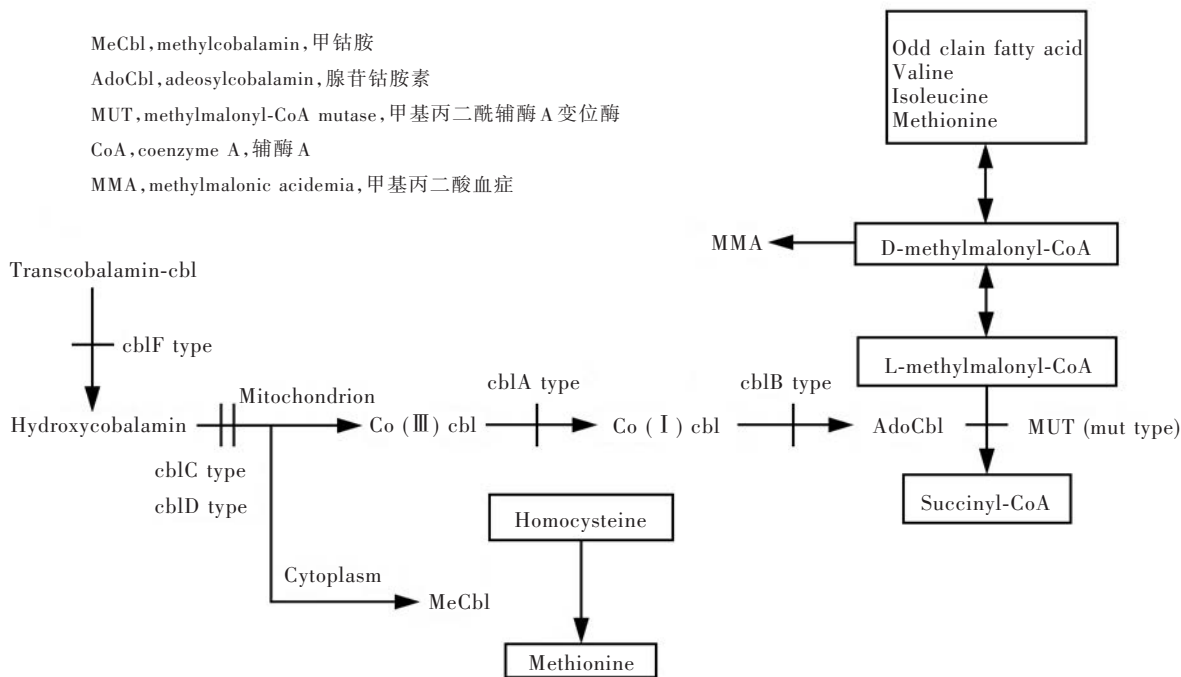


图5 维生素 B<sub>12</sub> 在细胞内代谢障碍累及环节以及甲基丙二酸血症各亚型<sup>[4]</sup>: cblA 型、cblB 型和 mut 型仅累及 AdoCbl 或 MUT 蛋白, 引起单纯甲基丙二酸血症; cblC 型、cblD 型和 cblF 型导致 AdoCbl 和 MeCbl 蛋白合成障碍, 引起甲基丙二酸血症合并高同型半胱氨酸血症

Figure 5 Links and different subtypes of MMA caused by intracellular metabolism disorder of vitamin B<sub>12</sub><sup>[4]</sup>. cblA type, cblB type and mut type only affect AdoCbl and MUT protein, and cause simple MMA. cblC type, cblD type and cblF type induce the disorder of anabolism of AdoCbl and MeCbl protein and result in MMA complicated with hyperhomocysteinemia.

表1 甲基丙二酸各亚型相关基因

Table 1. Different type of MMA and corresponding gene

Isolated MMA	Gene	Coding protein	Locus	OMIM
<b>MMA</b>				
cblA type	<i>MMAA</i>	Methylmalonic aciduria type A protein	4q31.21	251100
cblB type	<i>MMAB</i>	Cob ( I ) alamin adenosyltransferase	12q24	251110
mut type	<i>MUT</i>	Methylmalonyl-CoA mutase	6p12.3	251000
<b>Combined MMA and hyperhomocysteinemia</b>				
cblC type	<i>MMACHC</i>	Methylmalonic aciduria and homocystinuria type C protein	1p34.1	277400
cblD type	<i>MMADHC</i>	Methylmalonic aciduria and homocystinuria type D protein	2q23	277410
cblF type	<i>LMBRD1</i>	Putative lysosomal cobalamin exporter	6q13	277380
cblJ type	<i>ABCD4</i>	ATP-binding cassette subfamily	14q24	614857

MMA, methylmalonic acidemia, 甲基丙二酸血症; CoA, coenzyme A, 辅酶 A; OMIM, Online Mendelian Inheritance in Man, 在线人类孟德尔遗传数据库

习成绩下降、性格改变为首发症状, 病程中出现幻觉, 逐渐出现双下肢无力, 体格检查可见双下肢肌力下降、下肢深浅感觉对称性减弱、腱反射减退或消失等周围神经损害体征, 均支持晚发型甲基丙二酸血症的诊断, 进一步行遗传代谢性疾病的血浆氨基酸和酰基肉碱谱分析, 明确诊断。与既往文献报道的晚发型甲基丙二酸血症相似, 先证者之弟仅出

现学习成绩差、易怒等症状, 一直未引起重视, 待先证者明确诊断后, 行基因检测才确定亦存在 *MMACHC* 基因突变。先证者头部 MRI 突出表现为脑萎缩、白质髓鞘化不良, 与既往文献报道的甲基丙二酸血症典型影像学改变相符<sup>[13-16]</sup>。

*MMAcblC* 型致病基因为 *MMACHC* 基因, 定位于 1p34.1, 共包含 5 个外显子, 全长 10 800 bp, 编码

282 个氨基酸残端蛋白即 cblC 蛋白,该蛋白在催化维生素 B<sub>12</sub> 向 AdoCbl 和 MeCbl 转化过程中发挥重要作用<sup>[2]</sup>。本研究家系中先证者及其弟经基因检测明确诊断为 MMAcblC 型,系 *MMACHC* 基因复合杂合突变所致。其中, c.609G > A 为无义突变,可使第 203 位色氨酸转录提前终止,该变异位点为东亚地区最常见变异位点,占 40% ~ 60%<sup>[8,17-19]</sup>,该位点纯合突变多与早发型甲基丙二酸血症有关<sup>[19]</sup>; c.482G > A 为错义突变,可使第 161 位氨基酸由精氨酸突变为谷氨酰胺。Liu 等<sup>[17]</sup> 报告 8 例携带 c.482G > A 突变的患者,仅 1 例于 4 岁前发病,余均于 4 岁后发病,提示携带错义突变 c.482G > A 的患者临床表型多为晚发型。

本研究家系中先证者一经明确诊断即予甲钴胺、左卡尼汀治疗,早期即有效控制症状,治疗 3 个月复查血浆丙酰肉碱和 C3/C2 比值明显下降,提示为 MMAcblC 型。既往研究显示,多数晚发型 MMAcblC 型为维生素 B<sub>12</sub> 依赖型,建议早期肌肉注射或皮下注射维生素 B<sub>12</sub> (1 mg/d),同时予低蛋白饮食(每日蛋白质摄入量 < 0.80 g/kg),补充左旋肉碱 [50 ~ 100 mg/(kg·d)],提高蛋氨酸水平、降低同型半胱氨酸和甲基丙二酸水平,改善临床症状<sup>[4,20-21]</sup>。

晚发型甲基丙二酸血症临床罕见,但属可治性遗传性疾病,对维生素 B<sub>12</sub> 治疗反应良好,如果能够及时识别其不典型临床表现,通过特异性生物学指标和基因检测早期诊断、及时治疗,对患者预后意义重大。

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## The Annual Meeting of American Academy of Addiction Psychiatry 2017

Time: December 7–10, 2017

Venue: San Diego, California, USA

Website: [www.aaap.org/annual-meeting](http://www.aaap.org/annual-meeting)

The Annual Meeting of American Academy of Addiction Psychiatry 2017 will be held on December 7–10, 2017 in San Diego, California, USA. The Annual Meeting and Scientific Symposium provide the latest scientific developments in addiction psychiatry for physicians and allied health professionals who treat patients with substance use disorders (SUD) and mental health disorders. The meeting is structured to encourage interaction among clinicians from various disciplines, approaches and settings.

The Meeting aims to recognize emerging issues and trends in addiction psychiatry and be on the forefront of diagnosis and treatment of substance use disorders and co-occurring mental disorders. Participants should be able to: 1) identify how to recognize, diagnose, and treat substance use disorders as they change in society. 2) Increase their competency in using evidence based psychotherapy, medications and other treatments. 3) Improve their knowledge using didactic lectures, skill building workshops, and unique educational formats to support concepts in addiction psychiatry. 4) Increase skills to educate peers, colleagues, trainees, patients and the community about addiction psychiatry.

The Meeting can also provide support and education to addiction psychiatrists and clinicians treating patients with substance use disorders. Therefore, participants should be able to: 1) utilize and promote evidence-based approaches and current treatment guidelines for biopsychosocial treatment of substance use disorders and co-occurring mental disorders. 2) Network with peers and mentors to find support and guidance in the field of addiction psychiatry. 3) Develop and expand current educational curriculum in the field of addiction psychiatry.

The Meeting will demonstrate for trainees the various evidence-based approaches, treatments and settings applicable to the field (or practice) of addiction psychiatry. Trainees should be able to: 1) identify various career paths in addiction psychiatry available to them. 2) Increase their familiarity with career options and pathways by networking with leaders in addiction psychiatry. 3) Enhance their knowledge relevant to early careers in addiction psychiatry.

## The 142nd Annual Meeting of American Neurological Association

Time: October 15–17, 2017

Venue: San Diego, California, USA

Website: [2017.myana.org](http://2017.myana.org)

Abstract deadline: September 11, 2017

The 142nd Annual Meeting of American Neurological Association (ANA2017) will be held on October 15–17, 2017 in San Diego, California, USA. ANA2017 offers exceptional education, career development for all levels of academic neurology and networking opportunities with leaders in the field. Scientific symposia cover broad spectrum of subspecialties. Poster sessions are packed with the latest emerging neuroscience and interactive lunch workshops take breakout sessions to the next level.