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·临床病例讨论·

2例 *KCNT1* 基因突变婴儿癫痫伴游走性局灶性发作临床特点并文献复习

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[摘　要] 回顾性分析2例婴儿癫痫伴游走性局灶性发作(epilepsy of infancy with migrating focal seizures，EIMFS)患儿，分析其临床、头颅影像学及视频脑电图特点，采用二代测序癫痫基因检测包分析EIMFS的基因突变筛查结果，总结2例*KCNT1*基因突变致EIMFS的临床特点及基因特征。2例EIMFS患儿，均为男性，发作起病年龄为均在3个月内，2例均以游走性局灶性发作为主要发作类型，伴自主神经性发作。2例患儿均有频繁癫痫持续状态发生。视频脑电图特点：背景活动慢；发作间期主要表现为大量多灶性放电。头颅磁共振成像(magnetic resonance imaging，MRI)检查均伴异常。基因检测结果：1例为*KCNT1*基因c.862G>A(p.G288S)杂合突变，来源于母亲，1例为新发突变，c.1283G>A(p.R428Q)；2例均应用多种抗癫痫药治疗，1例应用丙种球蛋白针治疗，效果欠佳。EIMFS起病年龄早，发作类型均以游走性局灶性发作为主；多种抗癫痫药物治疗效果差。视频脑电图特征为发作间期大量多灶性放电，发作期为游走性多灶性放电。遗传性因素为该病主要病因，基因检测可协助诊断及指导遗传咨询，*KCNT1*基因突变为该病热点突变之一。

[关键词] 婴儿癫痫伴游走性局灶性发作；基因突变；临床特征

Clinical features of 2 infants with *KCNT1* gene mutation with epilepsy of infancy with migrating focal seizures and literature review

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Abstract Two epilepsy of infancy with migrating focal seizures (EIMFS) children was performed on retrospective analysis, the clinical, imaging and video electroencephalograms characteristics were analyzed. Candidate gene mutations were screened by next generation sequencing. The clinical and genetic characteristics of 2 cases of EIMFS caused by *KCNT1* gene mutation were summarized. Two patients were all males. Seizure onset age was within 3 months.

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Migrating focal seizure was presented, Autonomic manifestations were accompanied, etc. All patients had a history of status epilepticus. Corresponding EEG shows low-medium-amplitude fast waves that originated from some brain regions and migrated to other region. Cranial magnetic resonance imaging (MRI) was abnormal in 2 cases. Two cases carried heterozygous mutations of *KCNT1* gene, one of which was c.862G>A(p.G288S), from his mother, and the other was de novo c.1283G>A(p.R428Q). Both cases were treated with various antiepileptic drugs, and of one gamma globulin injection was used, with poor efficacy. EIMFS is clinically characterized by early onset, which is usually within 3 months after birth, migrating focal seizure. The interictal EEG shows multi-focal discharges, while the attack stage was migratory multifocal discharge. Genetic factors are the main causes of the disease, *KCNT1* gene mutation is one of the hot spot mutations of the disease.

Keywords epilepsy of infancy with migrating focal seizures; genes mutation; clinical manifestations

婴儿癫痫伴游走性局灶性发作(epilepsy of infancy with migrating focal seizures，EIMFS)是婴儿早期常见的癫痫性脑病之一。本病最早由意大利学者Coppola等[1]于1995年报道，被称为婴儿恶性游走性部分性发作(malignant migrating partial seizures of infancy，MMPSI)，2017年ILAE[2]将本病重新命名为EIMFS。其主要特征为新生儿或婴儿早期起病，无显著性别差异，男女均受累，游走性局灶性癫痫发作及严重的脑电图异常放电，伴精神运动发育迟滞或倒退，多种抗癫痫药物治疗效果差。该病病因及发病机制尚不明确，遗传性因素可能为主要病因之一。随二代测序基因检测方法的广泛应用，国内外有关本病的报道逐年增多，目前已发现10个致病基因*KCNT1*，*KCNQ2*，*SCN1A*，*SCN2A*，*SCN8A*，*PLCB1*，*SLC25A22*，*SLC12A5*，*TBC1D24*，*CHD2*基因均可导致本病。目前国内仅尚可为等[3]报道9例EIMFS患儿，现对郑州大学附属儿童医院2例*KCNT1*基因突变致EIMFS患儿的临床和脑电图特点以及基因诊断结果进行分析，以期提高对该病认识。

1 临床资料

参照Coppola等[4]描述的EIMFS的临床特点确定纳入标准：1)生后6个月内起病者；2)几乎持续的游走性的多种类型的局灶性发作者；3)发作期脑电图表现为多灶性放电，在一侧半球内或双侧半球之间游走，累及多个部位，临床发作与脑电图放电在时间和部位上密切相关者；4)逐渐进展的智力、运动发育倒退者；5)对抗癫痫药治疗反应不佳、预后不良者。排除标准：遗传代谢病和已知脑损伤病因导致的癫痫患者。纳入2017年2至3月郑州大学附属儿童医院收治的2例EIMFS患儿，分析其临床特征，相关生化检查，头颅影像学及神经电生理及基因检测结果，采用二代测序癫痫基因检测包筛查患儿的基因突变。采用一代测序的方法验证患儿及其父母相关突变位点。以“epilepsy of infancy with migrating focal seizures”“malignant migrating partial seizures of infancy”为关键词检索PubMed数据库中相关文献，进行阅读分析。

1.1 临床特征

2例患儿均为男性，起病年龄为12 d至2个月10 d，1例有癫痫家族史，2例围生期均未见明显异常，1例生后有病理性黄疸情况。临床发作以局灶性、游走性发作为特点，发作形式主要包括：眼球阵挛、头眼一侧斜视(左侧或右侧)、颜面发绀、呼吸暂停、流泪、瞳孔散大、局灶性发作继发全面性强直-阵挛发作、口部咀嚼症状。均有频繁癫痫持续状态发生。2例患儿均应用多种抗癫痫药物治疗，包括左乙拉西坦口服液、奥卡西平混悬液、德巴金口服液、托吡酯片、氯硝西泮片、苯巴比妥。1例应用奎尼丁治疗后临床发作减少80%以上，后逐渐停用其他抗癫痫药物。1例应用静脉注射人丙种球蛋白治疗，期间发作控制约1周。

1.2 辅助检查

2例患者血生化、血气分析、血氨、乳酸、同型半胱氨酸、铜蓝蛋白、尿遗传代谢筛查均在正常范围；例1血氨基酸及肉碱分析结果正常，例2患者戊二酰基肉碱含量轻度增高，但无明确临床意义。

表1 2例EIMFS患儿临床特征

Table 1 Clinical features of 2 patients with EIMFS

辅助检查	病例1	病例2
血生化、血气分析、血氨、乳酸、同型半胱氨酸、铜蓝蛋白	正常	正常
尿遗传代谢筛查	正常	正常
血氨基酸及肉碱分析结果	正常	戊二酰基肉碱含量轻度增高
视频脑电图(图1)	背景活动慢，醒-睡各期多灶性尖波、棘波发放，监测到数次电发作，监测到多次一个脑区起源的局灶运动性发作	背景活动慢，醒-睡各期多灶性尖波、棘波发放，监测到数次电发作，多次局灶运动性发作，局部脑区起源逐渐扩散至同侧半球→对侧半球
BAEP	双侧未见明显异常	双侧未见明显异常
VEP	双侧未见明显异常	双侧未见明显异常
基因检测(图2)	*KCNT1*新发突变，c.1283G>A(p.R428Q)	*KCNT1*杂合突变c.862G>A(p.G288S)，来源于母亲
头颅MRI(图3)	右侧大脑半球蛛网膜下腔增深，脑沟略宽	双侧额颞部蛛网膜下腔略宽，透明隔囊肿

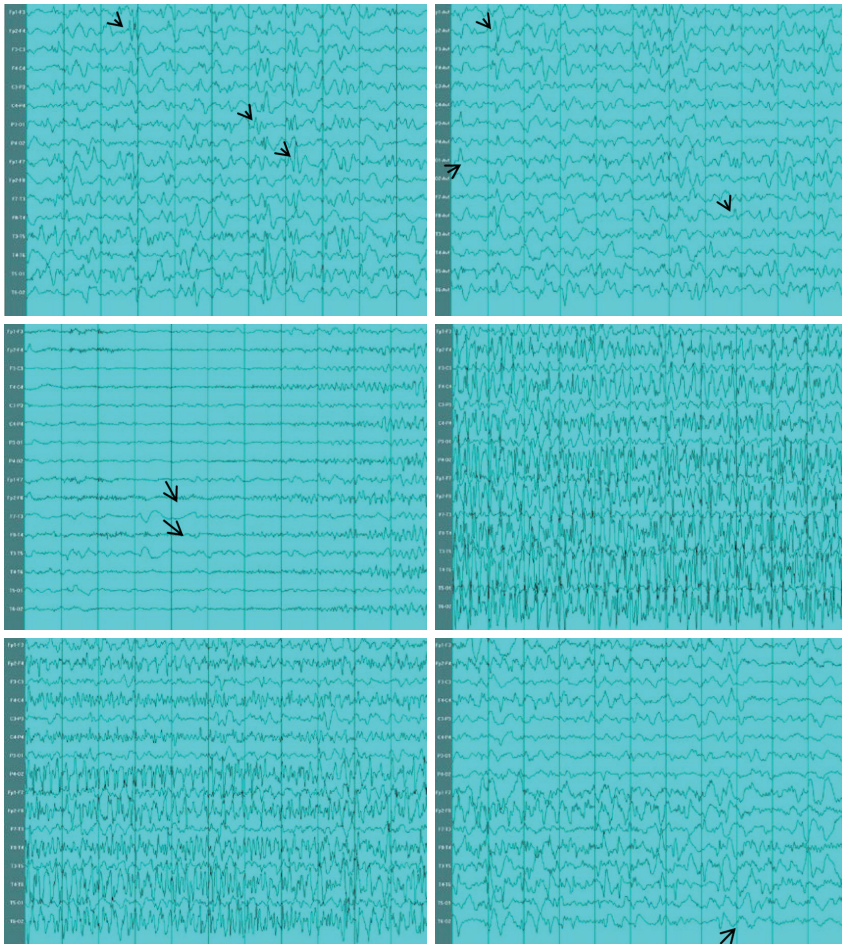

图1 例2脑电图示：游走性、多灶性放电

Figure 1 Patient 2: electroencephalogram shows illustrating migrating epileptic foci

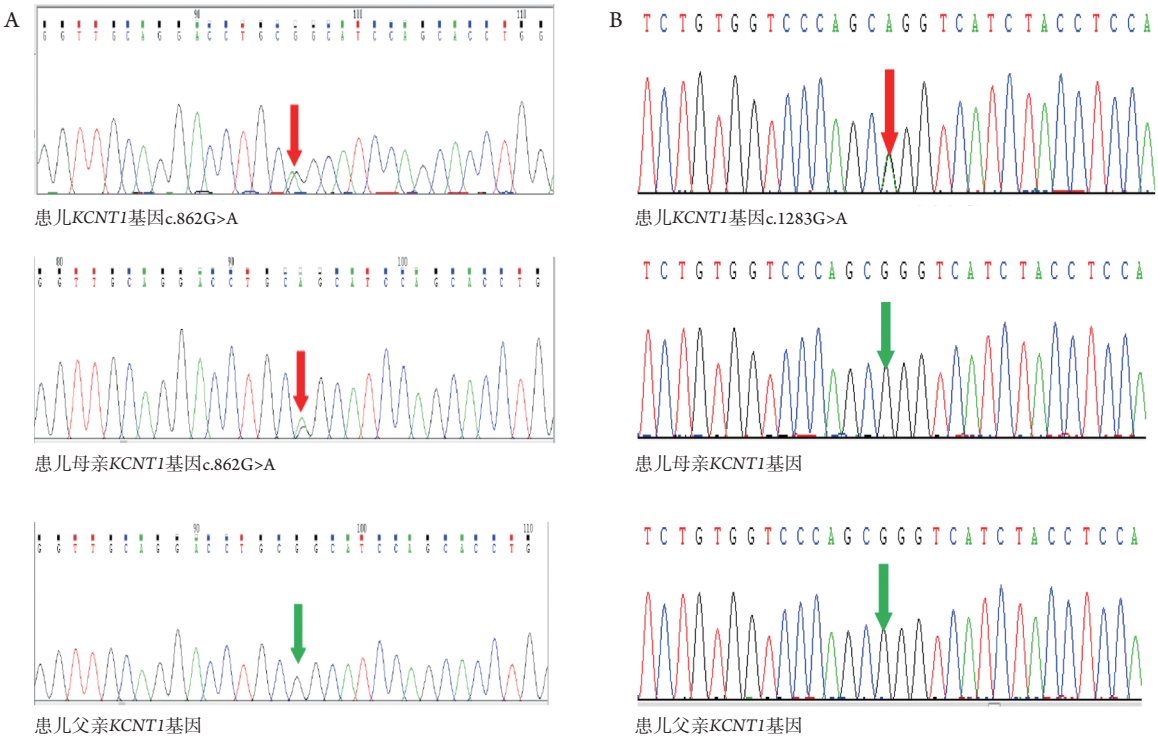

图2 EIMFS患儿及其父母基因测序图

Figure 2 Gene mutations of 2 patients with EIMFS and their parents

(A)例2患儿*KCNT1*基因c.862G>A(p.G288S)杂合突变，该突变来源于母亲，父亲无该位点突变；(B)例1患儿*KCNT1* 新发突变，c.1283G>A(p.R428Q)，患儿父、母均无该位点突变。

(A) *KCNT1* gene c.862G>A(p.G288S) heterozygous variation was found in patient 2 and his mother, and there was no variation in this site in his father; (B) *KCNT1* gene c.1283G>A(p.R428Q) de novo variation was found in patient 1, and there was no variation in this site in his parents.

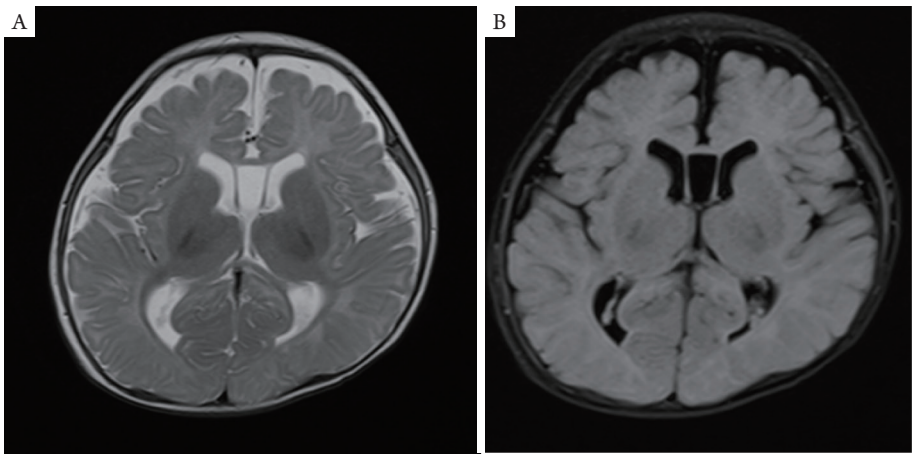

图3 例2患者(携带c.862G>A突变)头颅影像学结果示：双侧额颞部蛛网膜下腔增宽，透明隔囊肿

Figure 3 Brain magnetic resonance imaging of the patient 2(c.862G>A mutation) shows widened bilateral frontotemporal subarachnoid space, diagnosed as septum pellucidum cyst

(A)轴位T_2WI显示双侧额颞部蛛网膜下腔增宽，透明隔囊肿；(B)FLAIR像显示双侧额颞部蛛网膜下腔增宽，透明隔囊肿。

(A) Axial T_2WI shows widened bilateral frontotemporal subarachnoid space, diagnosed as septum pellucidum cyst; (B) Axial FLAIR shows widened bilateral frontotemporal subarachnoid space widened, diagnosed as septum pellucidum cyst.

1.3 视频脑电图

2例患儿脑电图均表现为背景活动减慢，发作间期：异常婴儿脑电图，醒-睡各期多灶尖波、棘波发放。发作期脑电图示：同期脑电表现为右侧或左侧1个或多个脑区起源的低波幅、低-中波幅快波，频率渐快，波幅渐高，可波及其他脑区或游走至对侧脑区，随后频率渐慢、波幅渐低(图1)。

1.4 基因检测结果

2例患儿均检测到*KCNT1*基因突变(图2)。

1.5 头颅 MRI 结果

例2患者(携带c.862G>A突变)头颅MRI结果示：双侧额颞部蛛网膜下腔增宽，透明隔囊肿(图3)。

2 讨论

EIMFS又称为婴儿恶性游走性部分性发作(malignant migrating partial seizures of infancy，MMPSI)，是婴儿早期常见的癫痫性脑病之一。该病发病率低，目前国内外共报道病例数大于100例。该病主要临床特征为起病年龄早，生后6个月内出现癫痫发作，持续局灶性游走性发作，发作形式多样，包括局灶性运动性发作和非运动性发作，其中自主神经性发作症状突出，6~9个月多进展为癫痫持续状态，发作期脑电图放电呈多灶性，背景活动减慢，病前头颅影像学检查可正常，精神运动发育迟滞或倒退，发作较难控制，预后差。

2017年国际抗癫痫联盟[5]将癫痫病因分为六大类(遗传性、代谢性、感染性、免疫性、结构性、病因未明)，该癫痫综合征病因尚不明确，离子通道相关基因突变可能是该病遗传因素之一。随着二代测序技术的广泛应用，截止目前，研究发现10种基因*KCNT1*，*KCNQ2*，*SCN1A*，*SCN2A*，*SCN8A*，*PLCB1*，*SLC25A22*，*SLC12A5*，*TBC1D24*，*CHD2*[6-14]均可导致本病发生。*KCNT1*突变在EIMFS中检出率最高，可能成为该病热点突变基因。

*KCNT1*基因位于9q34.3，包括31个外显子，编码钠离子门控钾离子通道的α亚基，目前为止最大的钾离子通道，含有1 235个氨基酸，其在脑组织中广泛表达，特别在额叶的表达更为显著。推测*KCNT1*基因突变致中间抑制神经元K^+通道电流增强，延长超极化时间，导致神经元兴奋性和抑制性失衡，从而导致癫痫发作[15]。KCNT1相关癫痫主要有两种表型：EIMFS和常染色体显性遗传的夜间额叶癫痫；少见临床表型包括：West综合征、大田原综合征、早期肌阵挛癫痫脑病、脑白质病或脑白质营养不良、局灶性癫痫等。

KCNT1相关EIMFS为常染色体显性遗传，多由新发突变或父母体细胞或生殖细胞嵌合体所致。临床出现以下症状时即高度提示EIMFS可能：1)产前过程无异常，出生时无缺氧、创伤、感染、血管性疾病相关性损伤；2)6个月前出现零星发作、局灶性不同步起源于不同半球的癫痫发作，随后频率逐渐增加；3)癫痫发作后出现发育停滞或倒退；4)药物治疗困难。KCNT1相关的EIMFS除神经系统受累外，还影响呼吸系统、心血管系统。Kawasaki等[16]研究发现：3例EIMFS患儿因主动脉-肺动脉侧枝动脉形式导致肺出血，发生于4~19个月。因此当患者出现呼吸衰竭、心力衰竭、咳血时需评估是否存在肺出血相关。

本组2例患者均检出该*KCNT1*基因突变，其中1例患者基因突变为杂合突变c.862G>A(p.G288S)，该突变来源于母亲，其母同有癫痫病史，临床表型与患儿不同，其母智力发育基本正常，无明显智力运动发育落后情况，同样基因突变临床表型为常染色体显性遗传夜间额叶癫痫。研究[17]显示：致病变异发生于KCNT1蛋白S5跨膜区域者临床表型多为EMIFS，在NAD^+连接域者，表型多为ADNFLE。另一例患者基因突变为杂合突变c.1283G>A(外显子13 p.R428Q)，为新发突变。研究[6,18]报道：该突变与该病相关，且为致病性突变。本研究2例患者在随访过程中均未发现肺出血、心律失常等情况。

EIMFS为婴儿期难治性癫痫综合征之一。多数患儿为药物难治性癫痫，本研究中2例患儿均应用3种以上抗癫痫药物治疗，其中1例应用丙种球蛋白治疗，临床发作难以控制。奎尼丁作为标签外用药，部分研究[6]显示KCNT1功能获得性基因突变应用奎尼丁治疗可能有效。随后有研究[19]显示其效果欠佳，且易导致心律失常，患儿4岁后奎尼丁治疗无效。由于其会导致致命性心律失常，其应用受到限制。本组患儿中1例应用奎尼丁治疗，发作减少80%以上，目前生长发育未见显著倒退，1例患儿随访12月时仍有频繁癫痫持续状态发生，随后失访。其他基因突变相关靶向治疗尚未报道。国内外有研究[20-21]显示：司替戊二醇联合氯硝西泮或氯巴占、左乙拉西坦、生酮饮食对部分患者有效，迷走神经刺激术证实无效。但缺乏长期大样本随访研究。典型临床表现有助于该病诊断，部分患者基因检测有助于明确诊断，为产前诊断提供帮助。

参考文献

1. Coppola G, Plouin P, Chiton C, et al. Migrating partial seizures in infancy: a malignant disorder with developmental arrest[J]. Epilepsia, 1995, 36(10): 1017-1024.
2. Fisher RS, Cross JH, French JA, et al. Operational classification of seizure types by the International League Against Epilepsy: position paper of the ILAE Commission for classification and terminology[J]. Epilepsia, 2017, 58(4): 522-530.
3. 尚可为, 张月华, 杨小玲, 等. 婴儿癫痫伴游走性局灶性发作的临床及基因突变特点[J]. 中华儿科杂志, 2016, 54(10): 735-739. SHANG Kewei, ZHANG Yuehua, YANG Xiaoling et al. Clinical features and gene mutations in epilepsy of infancy with migrating focal seizures[J]. Chinese Journal of Pediatrics, 2016, 54(10): 735-739.
4. Coppola G, Veggiotti P, Del Giudice EM, et al. Mutational scanning of potassium, sodium and chloride ion channels in malignant migrating partial seizures in infancy[J]. Brain Dev, 2006, 28(2): 76-79.
5. Coppola G. Malignant migrating partial seizures in infancy: an epilepsy syndrome of unknown etiology[J]. Epilepsia, 2009, 50(Suppl 5): 49-51.
6. Barcia G, Fleming MR, Deligniere A, et al. De novo gain of function KCNT1 channel mutations cause malignant migrating partial seizures of infancy[J]. Nat Genet, 2012, 44(11): 1255-1259.
7. Duan H, Peng J, Kessi M, et al. De novo KCNQ2 mutation in one case of epilepsy of infancy with migrating focal seizures That evolved to infantile spasms[J]. Child Neurol Open, 2018, 5: 2329048X18767738.
8. Carranza Rojo D, Hamiwka L, McMahon JM, et al. De novo SCN1A mutations in migrating partial seizures of infancy[J]. Neurology, 2011, 77(4): 380-383.
9. Howell KB, McMahon JM, Carvill GL, et al. SCN2A encephalopathy: a major cause of epilepsy of infancy with migrating focal seizures[J]. Neurology, 2015, 85(11): 958-966.
10. Ohba C, Kato M, Takahashi S, et al. Early onset epileptic encephalopathy caused by de novo SCN8A mutations[J]. Epilepsia, 2014, 55(7): 994-1000.
11. Poduri A, Chopra SS, Neilan EG, et al. Homozygous PLCB1 deletion associated with malignant migrating partial seizures in infancy[J]. Epilepsia, 2012, 53(8): e146-e150.
12. Poduri A, Heinzen EL, Chitsazzadeh V, et al. SLC25A22 is a novel gene for migrating partial seizures in infancy[J]. Ann Neurol, 2013, 74(6): 873-882.
13. Saito T, Ishii A, Sugai K, et al. A de novo missense mutation in SLC12A5 found in a compound heterozygote patient with epilepsy of infancy with migrating focal seizures[J]. Clin Genet, 2017, 92(6): 654-658.
14. Balestrini S, Milh M, Castiglioni C, et al. TBC1D24 genotype-phenotype correlation: epilepsies and other neurologic features[J]. Neurology, 2016, 87(1): 77-85.
15. Lim CX, Ricos MG, Dibbens LM, et al. KCNT1 mutations in seizure disorders: the phenotypic spectrum and functional effects[J]. J Med Genet, 2016, 53(4): 217-225.
16. Kawasaki Y, Kuki I, Ehara E, et al. Three cases of KCNT1 mutations: malignant migrating partial seizures in infancy with massive systemic to pulmonary collateral arteries[J]. J Pediatr, 2017, 191: 270-274.
17. Gertler T, Bearden D, Bhattacharjee A, et al. KCNT1-related epilepsy[D]. Seattle (WA): University of Washington, 2018.
18. Shimada S, Hirano Y, Ito S, et al. A novel KCNT1 mutation in a Japanese patient with epilepsy of infancy with migrating focal seizures[J]. Hum Genome Var, 2014, 1: 14027.
19. Abdelnour E, Gallentine W, McDonald M, et al. Does age affect response to quinidine in patients with KCNT1 mutations? Report of three new cases and review of the literature[J]. Seizure, 2018, 55: 1-3.
20. McTague A, Nair U, Malhotra S, et al. Clinical and molecular characterization of KCNT1-related severe early-onset epilepsy[J]. Neurology, 2018, 90: e55-e66.
21. Cilio MR, Bianchi R, Balestri M, et al. Intravenous levetiracetam terminates refractory status epilepticus in two patients with migrating partial seizures in infancy[J]. Epilepsy Res, 2009, 86: 66-71.

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