·儿童和青少年癫痫·

儿童和青少年癫痫相关局灶性皮质发育不良22例临床分析

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【摘要】 **研究背景**　局灶性皮质发育不良是一组包括皮质分层异常、细胞结构异常和细微白质异常的疾病，是难治性癫痫的主要病因。本研究总结儿童和青少年局灶性皮质发育不良的临床表现、脑电图和头部MRI特点，以期提高诊断与治疗水平。**方法**　回顾分析22例儿童和青少年局灶性皮质发育不良患者的临床表现、脑电图和头部MRI特点。**结果**　22例患者中13例(59.09%)单纯表现为局灶性发作，6例(27.27%)单纯表现为全面性发作，3例(13.64%)表现为局灶性发作继发全面性发作；发作频率较频繁，6例(27.27%)每日均有发作，13例(59.09%)≥1次/月，3例(13.64%)<1次/月；21例(95.45%)脑电图监测到异常慢波和痫样放电。12例MRI显示局灶性皮质发育不良位于额叶，头皮脑电图显示7例(7/12)局灶性额区异常慢波和痫样放电，2例(2/12)广泛性慢波和棘慢复合波，2例(2/12)颞区尖波，1例(1/12)中央中线少量尖波；单纯局灶性发作7例(7/12)，全面性发作4例(4/12)，局灶性发作继发全面性发作1例(1/12)。6例MRI显示局灶性皮质发育不良位于顶叶，头皮脑电图显示3例(3/6)局灶性顶区异常慢波和痫样放电，2例(2/6)颞枕区痫样放电，1例(1/6)无异常；单纯局灶性发作5例(5/6)，局灶性发作继发全面性发作1例(1/6)。2例MRI显示局灶性皮质发育不良位于颞叶，头皮脑电图显示1例(1/2)局灶性颞区异常慢波和痫样放电，1例(1/2)额区痫样放电；均为全面性发作。2例MRI显示局灶性皮质发育不良位于岛叶，头皮脑电图显示1例(1/2)双侧颞区痫样放电，1例(1/2)全导联尖波和尖慢复合波；单纯局灶性发作1例(1/2)，局灶性发作继发全面性发作1例(1/2)。**结论**　局灶性皮质发育不良患者通常于学龄前期和学龄期发病，主要呈现局灶性或全面性发作，亦可见其他发作类型，发作频率较频繁；头部MRI是诊断局灶性皮质发育不良的重要方法；治疗方法主要是抗癫痫药物，发作控制欠佳的患者考虑癫痫外科手术。

【关键词】 癫痫；　皮质发育畸形；　儿童；　青少年；　磁共振成像；　脑电描记术

Clinical analysis on 22 patients with childhood and juvenile epilepsy related focal cortical dysplasia

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【**Abstract**】 **Background**　Focal cortical dysplasia (FCD) is a group of diseases including abnormal cortical layer, abnormal cell structure and abnormal white matter. It is one of the main causes of intractable epilepsy. In this paper, the clinical manifestations, EEG and MRI characteristics of FCD in children and adolescents were summarized in order to improve the diagnosis and treatment level of clinicians. **Methods**　The clinical symptoms, EEG and MRI manifestations of 22 cases were retrospectively analyzed. **Results**　Among 22 cases, 13 cases (59.09%) only showed focal seizures, 6 cases (27.27%) only showed generalized seizures, and 3 cases (13.64%) showed focal to generalized seizures. The seizure frequency of 22 patients was namely: 6 cases (27.27%) had seizures daily, 13 cases (59.09%) were more than one time/month, and 3 cases (13.64%) were less than one time/month. EEG in 21 cases (95.45%) showed abnormal slow waves and epileptiform discharges. MRI of 12 cases showed FCD in

doi:10.3969/j.issn.1672-6731.2018.06.006

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frontal lobe, the scalp EEG of whom showed abnormal slow waves and epileptiform discharges in focal frontal region in 7 cases (7/12), extensive slow waves and spike and slow wave complex in 2 cases (2/12), temporal sharp waves in 2 cases (2/12), and a small amount of sharp waves at midline in one case (1/12). Simple focal seizures occurred in 7 cases (7/12), generalized seizures occurred in 4 cases (4/12), and focal to generalized seizures occurred in one case (1/12). MRI of 6 cases showed FCD in parietal lobe, the scalp EEG of whom showed abnormal slow waves and epileptiform discharges in focal parietal region in 3 cases (3/6), epileptiform discharges in temporo-occipital region in 2 cases (2/6), and no abnormality in one case (1/6). Simple focal seizures occurred in 5 cases (5/6), and focal to generalized seizures occurred in one case (1/6). MRI of 2 cases showed FCD in temporal lobe, the scalp EEG of whom showed abnormal slow waves and epileptiform discharges in focal temporal region in one case (1/2) and epileptiform discharges in frontal region in one case (1/2). Generalized seizures occurred in those 2 cases. MRI of 2 cases showed FCD in insular lobe, the scalp EEG of whom showed epileptiform discharges in bilateral temporal regions in one case (1/2) and sharp waves and sharp and slow wave complex of all lead in one case (1/2). Simple focal seizures occurred in one case (1/2) and focal to generalized seizures occurred in one case (1/2). **Conclusions** FCD mostly occurs in preschool and school age. Epileptic seizures are focal or generalized, other seizure type can also be seen, and the frequency is high. Head MRI is an important method for diagnosing FCD. Antiepileptic drugs (AEDs) therapy is mostly used to control epileptic seizures. Epilepsy surgeries should be considered if the curative effect of AEDs is poor.

【Key words】 Epilepsy; Malformation of cortial development; Child; Adolescent; Magnetic resonance imaging; Electroencephalography

局灶性皮质发育不良(FCD)最早于1971年由Taylor等[1]提出。局灶性皮质发育不良是一组疾病,包括皮质分层异常、细胞结构异常和细微白质异常[2-3],在儿童症状性癫痫中的发生率约为25%,且通常为难治性癫痫[4]。本研究回顾分析近2年北京大学第一医院诊断与治疗的22例儿童和青少年局灶性皮质发育不良患者的临床资料,总结其临床表现、脑电图和MRI特点,以期提高临床医师对疾病的认识及诊断与治疗水平。

临床资料

一、病例选择

1. 诊断标准 (1)癫痫的诊断均参照2017年国际抗癫痫联盟(ILAE)制定的诊断和分类标准[5-7]。(2)局灶性皮质发育不良的诊断和分型参照2011年国际抗癫痫联盟制定的诊断和分型标准[8-9],即FCD Ⅰ型,皮质分层异常(大多数FCD Ⅰ型MRI异常不明显且难以定位病变部位,明确诊断依靠病理学检查)。FCD Ⅱ型,局限性皮质发育障碍,MRI表现符合以下6项标准中的1项即可诊断,①皮质增厚。②灰白质交界区模糊。③皮质信号异常。④皮质下白质信号异常。⑤穿透现象。⑥脑沟异常。FCD Ⅲ型,伴其他先天性发育异常或围生期获得性异常,常通过MRI检查发现。局灶性皮质发育不良患者的临床症状与体征通常无特征性提示意义,FCD Ⅱ型和Ⅲ型可以依靠MRI诊断。(3)排除其他中枢神经系统疾病如颅内占位性病变、脑血管病、感染性、代谢性或中毒性疾病,以及精神病。

2. 一般资料 选择2015年2月–2017年2月在北京大学第一医院神经内科癫痫中心诊断与治疗的局灶性皮质发育不良患者共22例,男性12例,女性10例;年龄1~29岁,中位年龄16.68岁;发病年龄为2~20岁、中位发病年龄10岁,其中幼儿期(2岁)发病1例(4.54%)、成人早期(20岁)发病1例(4.54%)、学龄前期和学龄期发病20例(90.91%);病程0~19年,中位病程5.86年。本研究经北京大学第一医院道德伦理委员会审核批准,所有患者及其家属均知情同意并签署知情同意书。

二、临床表现

1. 临床症状 本组22例患者临床均表现为癫痫。(1)癫痫发作类型:22例患者中13例(59.09%)单纯表现为局灶性发作,6例(27.27%)单纯表现为全面性发作,3例(13.64%)表现为局灶性发作继发全面性发作。(2)癫痫发作频率:22例患者癫痫发作频率均较频繁,6例(27.27%)每日有发作,13例(59.09%)≥1次/月,3例(13.64%)<1次/月。

2. 脑电图特征 本组22例患者均行头皮脑电图监测,参照国际10-20标准放置19导联记录电极、参考电极置于双侧耳垂、增加蝶骨电极,检查参数:高频滤波70 Hz、低频滤波0.53 Hz,纸速30 mm/s,增

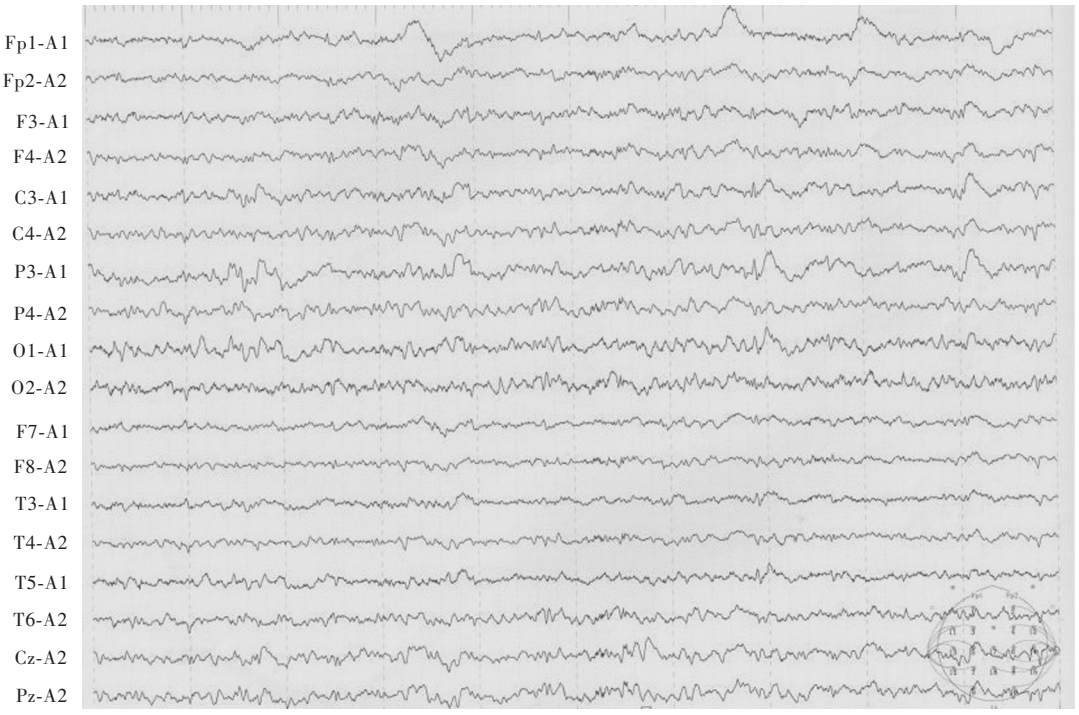


图1　男性患儿，年龄13岁，发病年龄12岁，表现为单纯局灶性发作，临床诊断为FCDⅡ型。头皮脑电图显示，左侧中央区和顶区棘慢复合波，尤以顶区显著

Figure 1　A 13-year-old boy with onset age of 12 years manifested as simple focal seizures and was diagnosed as FCD Ⅱ. The scalp EEG showed spike and slow wave complex in left central and parietal regions, especially in parietal region.

加过度换气试验。22例患者中10例(45.45%)背景活动正常；12例(54.55%)背景活动异常，包括背景α节律偏慢3例、背景出现慢波4例、双侧背景活动不对称5例。22例患者中21例(95.45%)监测到异常慢波和痫样放电，5例呈全导联广泛性异常；16例呈局限性异常，包括尖波、棘波、尖慢复合波和棘慢复合波等痫样放电(图1，2)。

3. MRI特征及局灶性皮质发育不良分型　本组22例患者均行头部MRI检查，采用美国GE公司生产的Signa 3.0T MRI扫描仪，明确诊断为局灶性皮质发育不良(图3，4)，其中FCDⅡ型20例(90.91%)。

4. 头部MRI病灶与脑电图异常部位和临床发作类型的关系　本组有12例患者MRI显示局灶性皮质发育不良位于额叶，头皮脑电图显示，7例(7/12)局灶性额区异常慢波和痫样放电，2例(2/12)广泛性慢波和棘慢复合波，2例(2/12)颞中区尖波，1例(1/12)中央中线少量尖波；单纯局灶性发作7例(7/12)，全面性发作4例(4/12)，局灶性发作继发全面性发作1例(1/12，表1)。本组有6例患者局灶性皮质发育不良位于顶叶，头皮脑电图显示，3例(3/6)局灶性顶区异常慢波和痫样放电，2例(2/6)颞枕区痫样放电，1例(1/6)未见异常；单纯局灶性发作5例(5/6)，局灶性发作继发全面性发作1例(1/6，表1)。本组有2例局灶性皮质发育不良位于颞叶，头皮脑电图显示，1例(1/2)局灶性颞区异常慢波和痫样放电，1例(1/2)额区痫样放电；2例均为全面性发作(表1)。本组有2例局灶性皮质发育不良位于岛叶，头皮脑电图显示，1例(1/2)双侧颞区痫样放电，1例(1/2)全导联尖波和尖慢复合波；单纯局灶性发作1例(1/2)，局灶性发作继发全面性发作1例(1/2，表1)。

三、治疗与转归

本组22例患者均予抗癫痫药物(AEDs)治疗，服用抗癫痫药物1～3种，平均2.18种。治疗后6个月随访，12例(54.55%)癫痫发作频率减少，10例(45.45%)无明显变化。

讨　论

脑在胚胎期发育过程中受损可以导致皮质发育畸形(MCD)，局灶性皮质发育不良是皮质发育畸

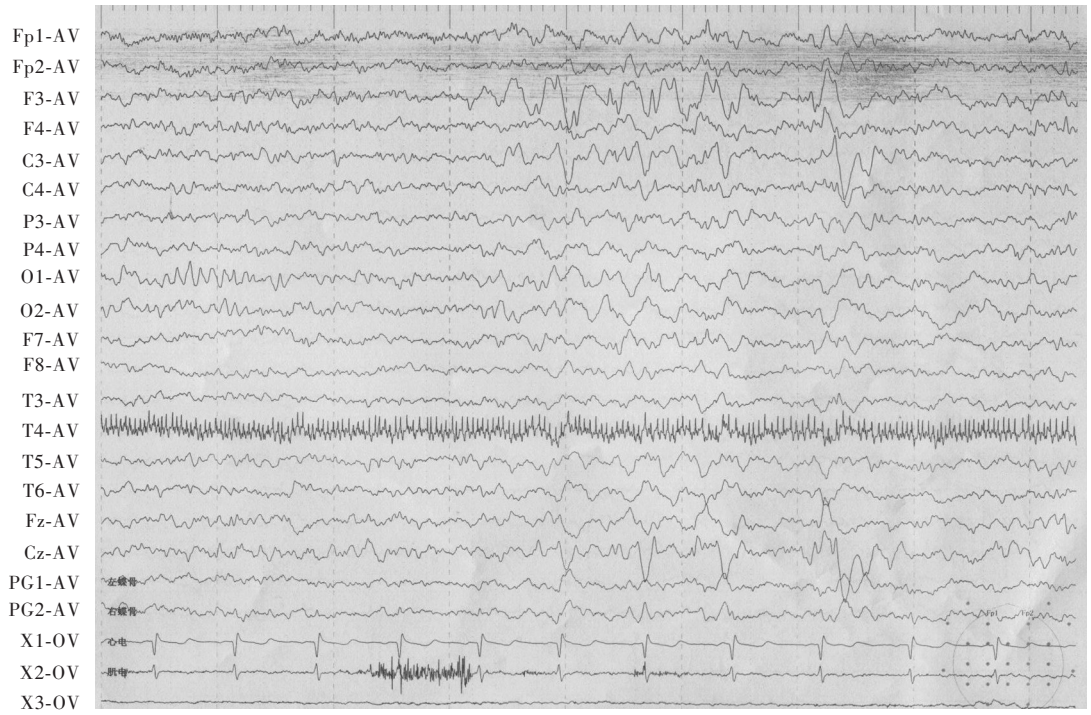


图2　女性患儿，年龄13岁，发病年龄13岁，表现为局灶性发作继发全面性发作，临床诊断为FCDⅢ型。头皮脑电图显示，左侧额区尖慢复合波

Figure 2　A 13-year-old girl with onset age of 13 years manifested as focal to generalized seizures and was diagnosed as FCDⅢ. The scalp EEG showed sharp and slow wave complex in left frontal region.

形的亚型，特点是皮质分层异常以及神经元迁移、增殖和分化异常。癫痫发作是局灶性皮质发育不良的最常见临床症状，与其解剖学结构异常有关[10-11]，在局灶性皮质发育不良区域存在神经元谷氨酸表达上调，且与周围皮质神经元存在异常联系。

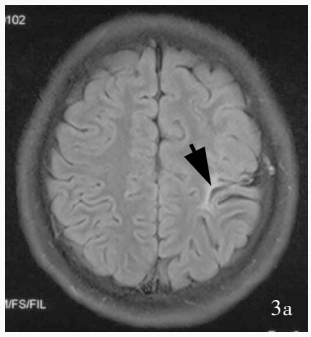
本研究揭示出局灶性皮质发育不良的部分临床特点，首先，发病年龄范围较大，婴幼儿和成人均可以发病，但以学龄前期和学龄期为主，与既往文献报道的局灶性皮质发育不良癫痫发作可以发生于任何年龄段但最常见于儿童期相一致[12-13]；其次，无明显性别差异，尚待更大样本量的临床研究进一步验证。

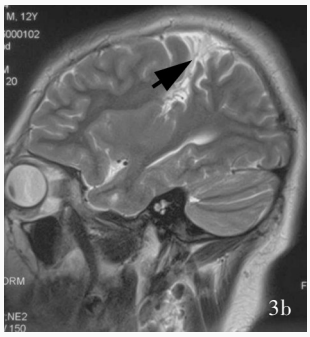
本组22例患者中仅1例发作间期脑电图正常，余21例发作间期脑电图均呈现异常，包括背景活动减慢，局限性痫样放电等，与既往研究者们观察到的局灶性皮质发育不良脑电图特点相一致[13-14]。约1/3的局灶性皮质发育不良患者头皮脑电图异常具有定侧和定位意义，病灶位于额叶的患者头皮脑电图出现额区痫样放电比例更高，且临床发作也常表现为额叶癫痫。

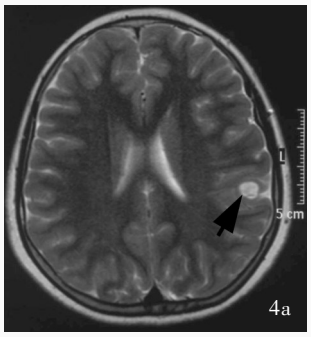
头部MRI是诊断局灶性皮质发育不良的重要方法，但是分型诊断具有一定困难。本组22例患者经MRI诊断为FCDⅡ型20例、FCDⅢ型2例。FCDⅡ型的MRI主要表现为皮质增厚、灰白质交界区模糊、皮质和皮质下白质信号异常、存在穿透现象、脑沟异常。FCDⅢ型2例，1例病灶位于额叶、1例位于顶叶，MRI表现与FCDⅠ型相似，同时伴其他先天性发育异常或围生期获得性异常。T_2WI和FLAIR成像常可发现细微异常，结合临床特点有助于诊断局灶性皮质发育不良[15-17]。

本研究进一步探讨头部MRI病灶与脑电图异常部位的关系，其中大部分患者（额叶8/12例，顶叶3/6例）MRI病灶与头皮脑电图异常部位相一致，亦有部分患者（4/12例）MRI病灶位于额叶而脑电图异常发生于颞顶区或枕区，究其原因，可能是由于头皮脑电图对痫样放电起源的监测存在局限性，或者局灶性皮质发育不良病灶存在功能障碍，而与之相隔较远的远隔区则成为激发的发作激活区并成为癫痫发作的起源部位[15-17]。

本研究局灶性皮质发育不良的治疗主要是抗癫痫药物，但随访6个月癫痫发作减少率仅54.55%（12/22）。有文献报道，局灶性皮质发育不良的癫痫







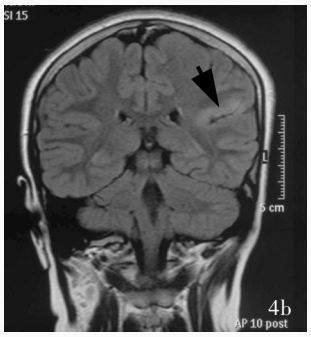


图3　图1患儿头部MRI检查所见　3a　横断面FLAIR成像显示，局灶性皮质发育不良跨中央沟灰质，呈高信号（箭头所示），脑回形态异常　3b　矢状位T_2WI显示，局灶性皮质发育不良跨中央沟灰质，呈高信号（箭头所示），脑回形态异常　**图4**　图2患儿头部MRI检查所见　4a　横断面T_2WI显示，左侧额叶类圆形囊性信号影（箭头所示），邻近皮质增厚　4b　冠状位FLAIR成像显示，左侧额叶下方脑回增厚伴异常信号影（箭头所示）

Figure 3　Head MRI findings of the child in Figure 1　Axial FLAIR revealed FCD with high-intensity signal across the central sulcus (arrow indicates) and abnormal cerebral gyri (Panel 3a). Sagittal T_2WI revealed FCD with high-intensity signal across the central sulcus (arrow indicates) and abnormal cerebral gyri (Panel 3b). **Figure 4**　Head MRI findings of the child in Figure 2　Axial T_2WI showed cystic abnormal signals (arrow indicates) of left frontal lobe and thickening of adjecent cortex (Panel 4a). Coronal FLAIR showed thickening of cerebral sulci with abnormal signals beneath the left frontal lobe (arrow indicates, Panel 4b).

表1　22例局灶性皮质发育不良患者头部MRI病灶与脑电图异常部位和临床发作类型的关系

Table 1.　Relationship between MRI lesions and EEG abnormalities and clinical features of 22 patients with FCD

Case	Clinical diagnosis	Lesion location of MRI	Abnormalities of EEG	Seizure
1	FCD Ⅱ	Right frontal lobe	Sharp and slow wave complex and spike waves in bilateral frontal poles, forehead, midline, bilateral anterior temporal lobes and sphenoidal electrodes	Focal seizures (FLE)
2	FCD Ⅱ	Left frontal lobe	Sharp waves, sharp and slow wave complex on left occipital and temporal lobes	Focal seizures (FLE)
3	FCD Ⅱ	Left frontal lobe	Sharp waves on left frontal pole, frontal lobe and frontal midline	Focal seizures
4	FCD Ⅱ	Left frontal lobe	Slow waves, sharp and slow wave complex on left frontal lobe	Generalized seizures
5	FCD Ⅲ	Left frontal lobe	Slow waves, sharp and slow wave complex on left frontal pole	Generalized seizures
6	FCD Ⅱ	Right frontal lobe	Rhythmic slow waves on left parietal lobe, sharp waves on left parietal lobe	Focal seizures
7	FCD Ⅱ	Right frontal lobe	Biphasic waves on right temporal lobe	Generalized seizures
8	FCD Ⅱ	Left frontal lobe	Slow waves on bilateral temporal lobes	Focal seizures
9	FCD Ⅱ	Left frontal lobe	Sharp waves on left occipital and posterior temporal lobes	Focal seizures
10	FCD Ⅱ	Right frontal lobe	Sharp waves on central line	Focal seizures
11	FCD Ⅱ	Right frontal lobe	Spike and slow wave complex on bilateral parietal lobes	Focal seizures Generalized seizures
12	FCD Ⅱ	Left frontal lobe	Spike and slow wave complex on bilateral parietal lobes	Generalized seizures
13	FCD Ⅱ	Left parietal lobe	Spike and slow wave complex on bilateral parietal lobes	Focal seizures
14	FCD Ⅱ	Right parietal lobe	Rhythmic slow waves on bilateral parietal lobes	Focal seizures
15	FCD Ⅱ	Right parietal lobe	Slow, complex, and three phase waves at right central, parietal and temporal lobes	Focal seizures
16	FCD Ⅲ	Right parietal lobe	Most of the right occipital and posterior temporal phases are three phase waves, sharp slow wave complex, negative phase sharp waves and sharp wave rhythm	Focal seizures Generalized seizures
17	FCD Ⅱ	Left parietal lobe	Normal	Focal seizures
18	FCD Ⅱ	Bilateral parietal lobes	The right anterior middle temporal and sphenoidal electrodes were released from cusp and sharp and slow wave complex	Focal seizures
19	FCD Ⅱ	Left temporal lobe	The left frontal pole, frontal, anterior middle temporal and sphenoidal electrodes were distributed by three phase, sharp and slow wave complex and sharp waves	Generalized seizures
20	FCD Ⅱ	Left ventricle posterior angle	Left frontal slow waves	Generalized seizures
21	FCD Ⅱ	Right insular lobe	A small amount of dyssynchrony wave in bilateral temporal regions and sphenoidal electrodes	Focal seizures
22	FCD Ⅱ	Left insular lobe	The total leads have more three phase waves, sharp and slow wave complex and negative phase sharp waves	Focal seizures Generalized seizures

FCD，focal cortical dysplasia，局灶性皮质发育不良；FLE，frontal lobe epilepsy，额叶癫痫

发作控制较为困难，抗癫痫药物治疗欠佳的患者可以考虑癫痫外科手术，但术后仍需药物辅助治疗，甚至有患者需反复多次进行癫痫外科手术治疗[18-19]。

综上所述，局灶性皮质发育不良是儿童和青少

年难治性癫痫的主要病因之一[19-20]，20世纪后期逐渐被广泛认识。本研究尚存在不足之处，如样本量较小，随访时间较短等。随着临床医师对局灶性皮质发育不良认识的深入，以及MRI和神经电生理学技术的迅速发展，将进行更多、试验设计更优良的大样本临床研究，进一步提高局灶性皮质发育不良的诊断与治疗水平。

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（收稿日期：2018-04-24）

下期内容预告 本刊2018年第7和8期报道专题为神经肌肉病，重点内容包括：应重视可治性神经肌肉病的早期诊断与治疗；我国Duchenne型肌营养不良症研究现状及存在问题；Duchenne型肌营养不良症治疗研究进展及应用前景；中国Duchenne型肌营养不良症诊断与治疗指南解读；Pompe病发展史；松软儿综合征；不同年龄段mdx小鼠骨骼肌能量代谢分析；Duchenne型肌营养不良症肌肉磁共振成像脂肪浸润和水肿特点分析；肢带型肌营养不良症2A型临床前期两例分析；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线粒体DNA 3243A>G突变率分析；核黄素反应性多种酰基辅酶A脱氢酶缺乏症临床表型及基因突变分析；Dysferlin肌病两家系临床表型及基因突变分析；*MTMR13/SBF2*基因复合杂合突变致腓骨肌萎缩症4B2型一家系临床表型及基因突变分析；短链脂酰辅酶A脱氢酶缺陷综合征一家系临床表型及遗传学分析；*GNE*基因新发突变致GNE肌病一例临床表型及生物信息学分析