·癫痫及发作性疾病·

发作性运动诱发性运动障碍神经回路研究进展

李资益 方侃 黄啸君 曹立

【摘要】 发作性运动诱发性运动障碍(PKD)是一类由突然动作诱发的以发作性不自主运动为特点的神经系统疾病。PKD患者基底节、丘脑和皮质等脑区之间存在结构或功能连接异常,基底节对丘脑的抑制功能减弱或丘脑自身功能障碍均可引起下游皮质的过度激活,产生不自主动作。小脑功能异常也在PKD的发病机制中发挥重要作用,小脑皮质异常可减弱其对小脑深部核团的正常抑制,同样导致丘脑-皮质通路的过度激活。本文综述PKD基底神经节-丘脑-皮质回路和小脑-丘脑-皮质回路的神经回路机制及研究进展,以提高临床医师对运动障碍性疾病发病机制的认识。

【关键词】 运动障碍; 神经传导; 综述

Advances on neural circuits of paroxysmal kinesigenic dyskinesia

LI Zi-yi[1], FANG Kan[1], HUANG Xiao-jun[2], CAO Li[1]

[1]*Department of Neurology, Shanghai Sixth People's Hospital Affiliated to Shanghai Jiaotong University School of Medicine, Shanghai 200233, China*

[2]*Department of Neurology, Ruijin Hospital, Shanghai Jiaotong University School of Medicine, Shanghai 200025, China*

Corresponding author: CAO Li (Email: caoli2000@yeah.net)

【Abstract】 Paroxysmal kinesigenic dyskinesia (PKD) is a kind of nervous system disease characterized by paroxysmal involuntary movements induced by sudden movements. Neuroimaging studies have found that there are structural changes or abnormal functional connectivity in the basal ganglia, thalamus, cortex and other brain regions in PKD patients. The weakened inhibitory and regulatory function of the basal ganglia to the thalamus or the dysfunction of the thalamus itself may cause over-activation of the cortical region, resulting in involuntary movements. Recent studies have found that abnormal cerebellar function plays an important role in the pathogenesis of PKD, and abnormal cerebellar cortex can affect its normal inhibitory effect on deep cerebellar nuclei, also leading to excessive activation of thalamic-cortical pathway. This paper reviewed the mechanism and research progress of PKD in recent years, mainly focusing on the basal ganglia-thalamic-cortical circuit and the cerebellar-thalamic-cortical circuit, so as to improve clinicians' understanding of the pathogenesis of movement disorders.

【Key words】 Motor disorders; Neural conduction; Review

This study was supported by the National Natural Science Foundation of China (No. 81870889), and "Three-year Action Plan for Promoting Clinical Skills and Clinical Innovation in Municipal Hospitals" Innovation and Transformation Ability Training Program for Research Physicians (No. SHDC2022CRD037).

Conflicts of interest: none declared

发作性运动诱发性运动障碍(PKD)系突然动作诱发的以发作性不自主运动为临床特点的发作性运动障碍性疾病,发作形式主要表现为肌张力障碍、舞蹈样动作、投掷样动作等一种或多种不自主运动[1-2]。PKD是最常见的发作性运动障碍,原发性PKD多与遗传因素相关,约25%患者有常染色体显性遗传家族史[3],富脯氨酸跨膜蛋白2(*PRRT2*)[4-6]和跨膜蛋白151A(*TMEM151A*)[7-9]为主要致病基因,此外个别患者中也发现*MR-1*、*SLC2A1*、*KCNA1*、*SCN8A*、*DEPDC5*、*CHRNA4*等基因变异[10-12];继发性

doi:10.3969/j.issn.1672-6731.2023.02.009

基金项目:国家自然科学基金资助项目(项目编号:81870889);"促进市级医院临床技能与临床创新三年行动计划"研究型医师创新转化能力培训项目(项目编号:SHDC2022CRD037)

作者单位:200233 上海交通大学医学院附属第六人民医院神经内科(李资益,方侃,曹立);200025 上海交通大学医学院附属瑞金医院神经内科(黄啸君)

通讯作者:曹立,Email:caoli2000@yeah.net

表1 PKD病理生理学机制相关临床研究

Table 1. Clinical study on pathophysiological mechanisms of PKD

文献来源	研究方法	男性（例）	女性（例）	平均年龄（岁）	研究结果
Mir等[20]（2005）	TMS，EMG	9	2	26.73	皮质-脊髓通路抑制功能障碍
Kang等[21]（2006）	TMS，EMG	10	2	19.42	皮质-脊髓通路抑制功能障碍
Shin等[22]（2010）	TMS，EMG	15	3	20.00	运动后阶段的周围抑制增强
Wei等[23]（2012）	周围神经电刺激，电生理监测	21	3	20.00	躯体感觉系统抑制功能减弱；皮质内、皮质下抑制回路异常
Luo等[24]（2013）	rs-fMRI	9	1	19.80	基底神经节-皮质回路自发性活动异常
Hsu等[25]（2013）	MEG	15	1	29.70	运动皮质运动后抑制作用减弱
Hsu等[26]（2013）	周围神经电刺激，MEG	14	1	30.30	初级、次级躯体感觉皮质内抑制异常
Kim等[27]（2015）	MRI	21	4	23.30	丘脑体积减少、形状改变、部分各向异性增加
Ren等[28]（2015）	rs-fMRI	8	3	18.95	基底神经节-丘脑-皮质回路和小脑半球之间静息态功能连接增强
Liu等[29]（2016）	rs-fMRI	21	11	19.88	皮质-基底神经节回路、楔前叶、额下回、角回自发性活动异常
Hsiao等[30]（2017）	周围神经电刺激，MEG	9	1	33.80	同侧初级躯体感觉皮质与对侧次级躯体感觉皮质、同侧与对侧次级躯体感觉皮质θ波功能连接减弱
Long等[31]（2017）	MRI，rs-fMRI	14	6	20.15	丘脑与运动皮质间功能连接与结构连接增强，丘脑与前额叶间功能连接减弱
Zhou等[32]（2018）	运动诱发试验，EMG	52	8	23.00	复合肌肉动作电位幅度增加，运动期肌细胞兴奋性异常
Liu等[33]（2018）	周围神经电刺激，MEG	15	4	24.37	初级躯体感觉皮质γ振荡同步率降低
Li等[34]（2019）	MRI	27	3	18.03	皮质脊髓通路平均扩散率下降，辅助运动前区以及额下回岛盖部灰质体积减少
Zhang等[35]（2020）	rs-fMRI	18	6	19.71	基底节、中央前回以及边缘系统节点中心度增加，颞极节点中心度下降
Li等[36]（2020）	MRI	64	14	23.07	白质结构连接整合性与隔离性下降，额下回、丘脑、梭状回、颞中回多处白质MRI参数异常
Li等[37]（2021）	MRI	71	16	23.00	灰质网络组织整合性与隔离性下降；基底节（尾状核、苍白球），丘脑，默认模式网络（扣带回后部、海马、额上回中部、角回、颞上回），中央执行网络（额上回背外侧、额中回、额下回、顶上回、缘上回）多处灰质核团MRI参数异常
Ekmen等[38]（2022）	MRI，rs-fMRI，TMS	14	8	29.40	运动小脑结构改变，小脑向丘脑信息传出异常
Kim等[39]（2022）	rs-fMRI	26	8	23.70	双侧丘脑和小脑自发性活动增强，丘脑与运动皮质之间功能连接增加

TMS，transcranial magnetic stimulation，经颅磁刺激；EMG，electromyography，肌电图；rs-fMRI，resting-state functional magnetic resonance imaging，静息态功能磁共振成像；MEG，magnetoencephalography，脑磁图

PKD主要见于多发性硬化（MS）[13]、脑组织钙化[14-15]和代谢异常[16-19]等疾病。PKD的病理生理学机制尚不明确，存在基底节、丘脑、大脑皮质、小脑等脑区功能异常（表1）[20-39]。本文拟综述PKD神经回路研究进展并提出可进一步探索的脑区或神经回路，以提高对运动障碍性疾病发病机制的认识。

一、基底神经节-丘脑-皮质回路异常

PKD呈发作性且抗癫痫药物（AEDs）对部分患者有效，故既往被认为是一种癫痫亚型[40]。但是PKD多表现为非固定肢体的肌张力障碍和舞蹈样动作，并非完全符合癫痫反复、刻板的发作特点，且部分患者对左旋多巴和丁苯那嗪等锥体外系疾病治疗药物反应较好[41-42]，提示PKD可能是一种锥体外系疾病。锥体外系主要包括皮质-纹状体系统和皮质-脑桥-小脑系统，基底神经节-丘脑-皮质回路异常被认为是肌张力障碍和舞蹈症患者产生不自主运动的主要机制之一。纹状体作为基底神经节信息输入核团，接收来自大脑皮质的运动指令，并直接向苍白球内侧部（Gpi）和黑质网状部（SNr）传递抑制性投射，该途径称为直接通路；或者通过苍白球外侧部（Gpe）和丘脑底核（STN）将运动指令传递至苍白球内侧部或黑质网状部，该途径称为间接通路，苍白球内侧部或黑质网状部再将抑制性投射传递至丘脑，调控大脑皮质运动区兴奋性及下游皮质脊髓束传导通路，进而调节肌肉收缩与运动[43]（图1a）；此外，丘脑底核还可以直接接收来自大脑皮质的运动指令以调控苍白球内侧部或黑质网状部，该通路称为超直接通路[44]。基底神经节抑制性输出障碍导致下游丘脑-皮质回路过度兴奋被认为是产生过度运动的原因[45-46]（图1b）。

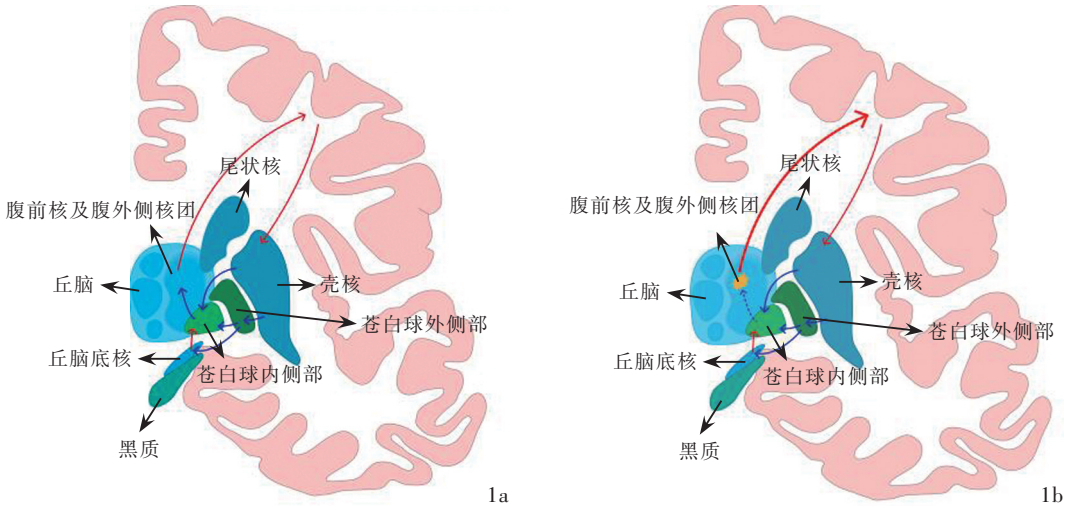

图1 基底神经节-丘脑-皮质回路(SciDRAW网站,https://www.scidraw.io/) 1a 基底节接收大脑皮质运动指令,经直接通路或间接通路调控丘脑,进而调控大脑皮质运动区(红色箭头代表兴奋性传递,蓝色箭头代表抑制性传递) 1b 基底节对丘脑的抑制作用减弱或丘脑功能障碍导致运动皮质异常激活,产生不自主运动(红色箭头代表兴奋性传递,蓝色箭头代表抑制性传递;红色粗箭头代表功能增强,蓝色虚箭头代表功能减弱)

Figure 1 Basal ganglia-thalamic-cortical circuit by SciDRAW website (https://www.scidraw.io/) After receiving the motor instruction of the cerebral cortex, the basal ganglia regulates the thalamus through direct or indirect pathway, and then regulates the motor area of the cerebral cortex (red arrows indicate excitatory transmission, blue arrows indicate inhibitory transmission; Panel 1a). Decreased inhibition of the basal ganglia on the thalamus or thalamic dysfunction leads to abnormal activation of the motor cortex to produce involuntary movement (red arrows indicate excitatory transmission, blue arrows indicate inhibitory transmission; thick red arrow indicates increased functionality, dashed blue arrow indicates decreased functionality; Panel 1b).

随着影像学技术的进步,MRI和fMRI广泛应用于PKD研究。PKD患者丘脑部分各向异性(FA)和平均扩散率(MD)显著变化,提示丘脑微结构发生改变[47]。PKD患者双侧壳核和左侧中央后回低频振荡振幅(ALFF)增加,表明基底节区及皮质部分区域存在自发性活动异常[48],尤其是辅助运动区、前运动皮质和壳核,且丘脑与运动皮质功能连接(FC)和结构连接(SC)显著增强[24,31]。继发于双侧基底节区和丘脑钙化的继发性PKD临床并不少见,同样支持基底神经节-丘脑-皮质回路在PKD发病机制中具有重要作用[14,49]。Saiki等[18]报告1例继发于糖尿病的PKD患者,SPECT显示对侧额叶高灌注、基底节区低灌注,纠正血糖至正常水平后不自主运动消失且脑灌注恢复正常;Murakami等[50]报告一PKD家系,接受分期双侧丘脑腹嘴核毁损术后发作症状有不同程度改善。尽管基底节、丘脑和皮质功能异常在PKD的发病机制中具有重要作用,但需关注的是,基底节是否为PKD病理生理学机制起源点?一项氢质子磁共振波谱(^{1}H-MRS)分析PKD患者脑组织代谢物变化的研究显示,基底节区胆碱复合物减少[51],基底节区胆碱能中间神经元可整合来自皮质和丘脑的信息以及纹状体内各种神经信号[52],胆碱能递质水平异常可导致基底节功能障碍,诱发异常运动,这一机制已在亨廷顿病和肌张力障碍患者中得到验证[53-54],但该项研究仅纳入5例PKD患者,样本量较小,且并未探究PKD基底节功能异常的分子机制。*PRRT2*作为PKD最常见的致病基因,其编码的PRRT2蛋白除在大脑皮质和小脑高表达外,在基底节和丘脑也有表达[55],相关研究主要集中于大脑皮质功能异常。*PRRT2*基因敲除大鼠初级运动皮质可溶性N-乙基马来酰亚胺敏感因子连接物复合体(SNARE)表达水平显著升高,初级运动皮质神经递质释放增加,神经元兴奋性增高,表现为自发性运动诱发性舞蹈样动作,但在小脑或海马组织中未观察到这一现象[56]。早期针对PKD的神经电生理学研究显示,前臂屈肌与前臂伸肌之间交互抑制功能减弱,且皮质内抑制亦减弱[20-21,57],提示皮质和脊髓抑制回路异常。Hsiao等[30]采用脑磁图观察躯体感觉网络内各脑区功能连接的变化,发现PKD患者对侧初级躯体感觉区与同侧次级躯体感觉区连接减弱,但双侧次级躯体感觉区之间连接增强。突发的自主动作可激活外周感觉信号传入,皮质功能异

常如皮质内抑制减少则使兴奋在皮质内异常扩散，这可能是引起运动障碍的主要作用机制。感觉皮质异常还可能与发作前预感有关，大脑皮质不仅是周围信息接收和整合中心，也是组织和传递命令的中心，皮质功能异常可导致纹状体或小脑通路功能障碍，或直接产生异常的皮质-脊髓传出，但具体作用机制尚不完全清楚。

二、小脑-丘脑-皮质回路异常

*PRRT2*基因在小脑高表达，主要富集于颗粒细胞（GC）[55,58-59]。动物模型显示，光刺激*PRRT2*基因变异小鼠小脑神经元可诱发运动障碍[55,59]；特异性敲除颗粒细胞*PRRT2*基因的小鼠出现平衡木行走障碍和高温诱发的运动障碍，但在敲除前脑（运动皮质和纹状体）*PRRT2*基因的小鼠中未观察到这一现象[55]，提示小脑更有可能是PKD的原发病灶，尤其是*PRRT2*基因变异导致的PKD。*PRRT2*基因敲除小鼠颗粒细胞胞膜钠离子通道数量增加，颗粒细胞兴奋性显著增强。小脑颗粒细胞通过苔藓纤维（MF）接收信息，并传递给浦肯野细胞（PC），细胞电生理学模型显示，刺激信息传入小脑切片苔藓纤维时，颗粒细胞电活动更加活跃[60]，此外，小脑分子层突触小泡数量也有所增加，颗粒细胞轴突所组成的平行纤维（PF）与浦肯野细胞之间的突触传递更活跃[55]。特异性敲除小鼠颗粒细胞*PRRT2*基因，可见浦肯野细胞呈现异常电活动，其自发放电频率增加，光刺激后放电频率进一步增加，约5秒后出现长达20秒的刺激后抑制，谷氨酸受体阻断剂可纠正浦肯野细胞异常放电模式[55]。亦有研究显示，电刺激*PRRT2*基因敲除小鼠平行纤维，平行纤维与浦肯野细胞之间的突触传递减弱，浦肯野细胞放电频率减少[58]，提示刺激方式不同（光刺激和电刺激）研究结果差异较大，但可确定的是*PRRT2*基因变异影响颗粒细胞并最终导致浦肯野细胞兴奋性异常。浦肯野细胞是小脑皮质神经元向小脑深部核团（DCN）发出的可传出神经冲动的唯一神经元，主要作用是抑制小脑深部核团的兴奋性[61]。*PRRT2*基因变异小鼠发生小脑皮质扩散性去极化（SD），可抑制浦肯野细胞电活动，干扰小脑深部核团正常放电，部分小脑深部核团神经元放电频率短时间内显著增加，随后出现十余秒抑制；且小脑深部核团异常放电模式与小鼠运动障碍发作时间相对应[59]。临床研究方面，Ekmen等[38]对22例*PRRT2*基因变异致PKD患者进行MRI和fMRI研究，双侧小脑第Ⅵ小叶灰质体积减少，且发病越早、左侧小脑第Ⅵ小叶和双侧小脑Crus Ⅰ区灰质体积越小，病程越长、小脑Crus Ⅱ区灰质体积越小；他们同时采用基于Fixel分析（FBA）对全脑DWI图像进行分析，发现小脑上脚和中脚近端纤维密度和小脑第Ⅵ小叶纤维束横截面积增大，表明小脑及小脑相关通路中存在轴突生长异常，使纤维束信息传递能力减弱；进一步行动态因果模型（DCM）分析，PKD患者小脑向丘脑信息传出功能障碍，小脑第Ⅷ小叶对丘脑的抑制作用减弱、第Ⅵ小叶对丘脑的兴奋作用减弱、第Ⅵ小叶的自我抑制作用增强，丘脑至纹状体以及丘脑至初级运动皮质的兴奋性传递增强；此外，他们还采用经颅磁刺激（TMS）PKD患者小脑，刺激后动态因果模型显示，丘脑-纹状体连接和丘脑-皮质有效连接接近健康对照者水平。Kim等[39]发现，PKD患者双侧丘脑和小脑第Ⅷ小叶分数低频振荡振幅（fALFF）显著增加，表明两个脑区自发活动增强，同时发现丘脑与其同侧运动皮质功能连接增强，且病程与功能连接强度呈正相关，证实丘脑-皮质连接异常参与PKD的发病机制，但该项研究未对小脑与其他脑区之间的功能连接进行分析。

小脑可整合来自皮质的感觉和运动信息，并通过丘脑反馈调节运动皮质。目前认为，浦肯野细胞通过抑制小脑深部核团传出过程以调控小脑深部核团对丘脑及其与大脑皮质和纹状体之间的信息传递，以辅助运动的计划与执行[62]（图2a）。多数*PRRT2*基因变异可导致PRRT2蛋白功能丧失，使颗粒细胞和浦肯野细胞异常兴奋，导致小脑输出核团功能异常。颗粒细胞兴奋性增强可能导致小脑皮质对小脑深部核团的抑制减少，使丘脑-皮质通路过度兴奋，从而产生过度运动（图2b）。由此可见，小脑很可能是PKD的发病起源，尤其是*PRRT2*基因变异患者，但小脑结构和功能异常是否同样是非*PRRT2*基因变异致PKD的病理生理学机制，尚待进一步证实。

三、小结与展望

目前PKD研究主要集中于基底神经节-丘脑-皮质回路和小脑-丘脑-皮质回路这两条主要的神经回路，大多数患者常伴随抑郁、焦虑、恐惧等情绪[63]。PKD患者处于压力或疲劳状态时更易发作或发作频率增加，部分患者颞极、边缘系统、小脑等与情绪产生和处理相关的脑区存在功能异常[35-37]。但因对PKD患者情绪关注度较低，且缺乏一致性评价标

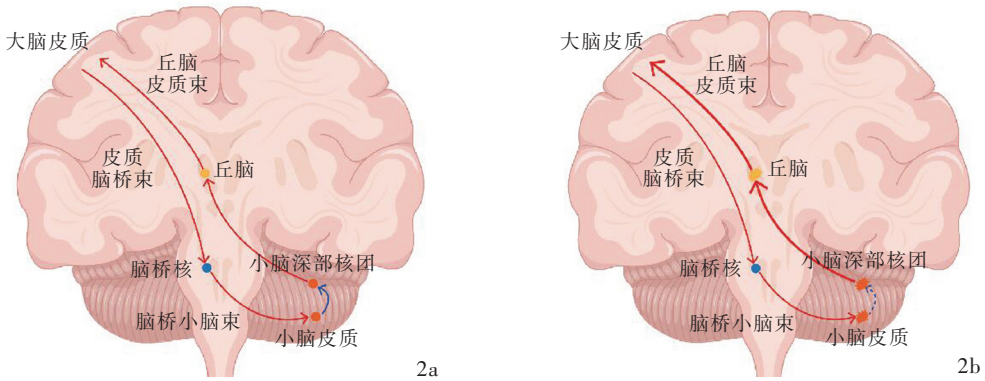

图2 小脑-丘脑-皮质回路(本图由Figdraw绘制) 2a 大脑皮质通过脑桥核向小脑传递运动和感觉信息,小脑皮质整合后传递抑制性投射至小脑深部核团,调控与丘脑和大脑皮质之间的信息传递(红色箭头代表兴奋性传递,蓝色箭头代表抑制性传递) 2b 小脑皮质内神经元兴奋性增强,对小脑深部核团的抑制作用减弱,小脑深部核团神经电活动异常,导致丘脑-皮质通路异常兴奋,产生不自主动作(红色箭头代表兴奋性传递,蓝色箭头代表抑制性传递;红色粗箭头代表功能增强,蓝色虚箭头代表功能减弱)

Figure 2 Cerebellar-thalamo-cortical circuit by Figdraw The cerebral cortex transmits motor and sensory information to the cerebellum through the pontine nuclei, and the cerebellar cortex integrates and transmits inhibitory projections to the deep cerebellar nuclei (DCN), regulating the transmission of information between the thalamus and cerebral cortex (red arrows indicate excitatory transmission, blue arrows indicate inhibitory transmission; Panel 2a). The excitability of neurons in the cerebellar cortex is abnormally increased, and the inhibitory effect on the DCN is weakened. The abnormal electrical activity of the DCN leads to abnormal excitation of thalamic-cortical pathway and involuntary movements (red arrows indicate excitatory transmission, blue arrows indicate inhibitory transmission; thick red arrows indicate increased functionality, dashed blue arrow indicates decreased functionality; Panel 2b).

准,目前尚无针对PKD情绪相关神经回路的研究。情绪是影响PKD发作频率、疾病严重程度和生活质量的重要因素[63],深入探究运动症状与非运动症状之间的关系以及PKD异常情绪的产生机制将有助于更全面地了解PKD的致病机制。

利益冲突 无

参 考 文 献

[1] Bruno MK, Hallett M, Gwinn-Hardy K, Sorensen B, Considine E, Tucker S, Lynch DR, Mathews KD, Swoboda KJ, Harris J, Soong BW, Ashizawa T, Jankovic J, Renner D, Fu YH, Ptacek LJ. Clinical evaluation of idiopathic paroxysmal kinesigenic dyskinesia: new diagnostic criteria[J]. Neurology, 2004, 63:2280-2287.

[2] Cao L, Huang X, Wang N, Wu Z, Zhang C, Gu W, Cong S, Ma J, Wei L, Deng Y, Fang Q, Niu Q, Wang J, Wang Z, Yin Y, Tian J, Tian S, Bi H, Jiang H, Liu X, Lü Y, Sun M, Wu J, Xu E, Chen T, Chen T, Chen X, Li W, Li S, Li Q, Song X, Tang Y, Yang P, Yang Y, Zhang M, Zhang X, Zhang Y, Zhang R, Ouyang Y, Yu J, Hu Q, Ke Q, Yao Y, Zhao Z, Zhao X, Zhao G, Liang F, Cheng N, Han J, Peng R, Chen S, Tang B. Recommendations for the diagnosis and treatment of paroxysmal kinesigenic dyskinesia: an expert consensus in China[J]. Transl Neurodegener, 2021, 10:7.

[3] Huang XJ, Wang SG, Guo XN, Tian WT, Zhan FX, Zhu ZY, Yin XM, Liu Q, Yin KL, Liu XR, Zhang Y, Liu ZG, Liu XL, Zheng L, Wang T, Wu L, Rong TY, Wang Y, Zhang M, Bi GH, Tang WG, Zhang C, Zhong P, Wang CY, Tang JG, Lu W, Zhang RX, Zhao GH, Li XH, Li H, Chen T, Li HY, Luo XG, Song YY, Tang HD, Luan XH, Zhou HY, Tang BS, Chen SD, Cao L. The phenotypic and genetic spectrum of paroxysmal kinesigenic dyskinesia in China[J]. Mov Disord, 2020, 35:1428-1437.

[4] Chen WJ, Lin Y, Xiong ZQ, Wei W, Ni W, Tan GH, Guo SL, He J, Chen YF, Zhang QJ, Li HF, Lin Y, Murong SX, Xu J, Wang N, Wu ZY. Exome sequencing identifies truncating mutations in PRRT2 that cause paroxysmal kinesigenic dyskinesia[J]. Nat Genet, 2011, 43:1252-1255.

[5] Cao L, Huang XJ, Zheng L, Xiao Q, Wang XJ, Chen SD. Identification of a novel PRRT2 mutation in patients with paroxysmal kinesigenic dyskinesias and c. 649dupC as a mutation hot-spot[J]. Parkinsonism Relat Disord, 2012, 18:704-706.

[6] Méneret A, Grabli D, Depienne C, Gaudebout C, Picard F, Dürr A, Lagroua I, Bouteiller D, Mignot C, Doummar D, Anheim M, Tranchant C, Burbaud P, Jedynak CP, Gras D, Steschenko D, Devos D, Billette de Villemeur T, Vidailhet M, Brice A, Roze E. PRRT2 mutations: a major cause of paroxysmal kinesigenic dyskinesia in the European population[J]. Neurology, 2012, 79:170-174.

[7] Tian WT, Zhan FX, Liu ZH, Liu Z, Liu Q, Guo XN, Zhou ZW, Wang SG, Liu XR, Jiang H, Li XH, Zhao GH, Li HY, Tang JG, Bi GH, Zhong P, Yin XM, Liu TT, Ni RL, Zheng HR, Liu XL, Qian XH, Wu JY, Cao YW, Zhang C, Liu SH, Wu YY, Wang QF, Xu T, Hou WZ, Li ZY, Ke HY, Zhu ZY, Zheng L, Wang T, Rong TY, Wu L, Zhang Y, Fang K, Wang ZH, Zhang YK, Zhang M, Zhao YW, Tang BS, Luan XH, Huang XJ, Cao L. TMEM151A variants cause paroxysmal kinesigenic dyskinesia: a large-sample study[J]. Mov Disord, 2022, 37:545-552.

[8] Wirth T, Méneret A, Drouot N, Rudolf G, Lagha Boukbiza O, Chelly J, Tranchant C, Piton A, Roze E, Anheim M. De novo mutation in TMEM151A and paroxysmal kinesigenic dyskinesia [J]. Mov Disord, 2022, 37:1115-1117.

[9] Li HF, Chen YL, Zhuang L, Chen DF, Ke HZ, Luo WJ, Liu GL, Wu SN, Zhou WH, Xiong ZQ, Wu ZY. TMEM151A variants cause paroxysmal kinesigenic dyskinesia [J]. Cell

Discov, 2021, 7:83.
[10] Wang HX, Li HF, Liu GL, Wen XD, Wu ZY. Mutation analysis of MR - 1, SLC2A1, and CLCN1 in 28 PRRT2 - negative paroxysmal kinesigenic dyskinesia patients[J]. Chin Med J (Engl), 2016, 129:1017-1021.
[11] Yin XM, Lin JH, Cao L, Zhang TM, Zeng S, Zhang KL, Tian WT, Hu ZM, Li N, Wang JL, Guo JF, Wang RX, Xia K, Zhang ZH, Yin F, Peng J, Liao WP, Yi YH, Liu JY, Yang ZX, Chen Z, Mao X, Yan XX, Jiang H, Shen L, Chen SD, Zhang LM, Tang BS. Familial paroxysmal kinesigenic dyskinesia is associated with mutations in the KCNA1 gene[J]. Hum Mol Genet, 2018, 27:625-637.
[12] Tian WT, Huang XJ, Mao X, Liu Q, Liu XL, Zeng S, Guo XN, Shen JY, Xu YQ, Tang HD, Yin XM, Zhang M, Tang WG, Liu XR, Tang BS, Chen SD, Cao L. Proline - rich transmembrane protein 2 - negative paroxysmal kinesigenic dyskinesia: clinical and genetic analyses of 163 patients[J]. Mov Disord, 2018, 33: 459-467.
[13] Baguma M, Ossemann M. Paroxysmal kinesigenic dyskinesia as the presenting and only manifestation of multiple sclerosis after eighteen months of follow-up[J]. J Mov Disord, 2017, 10:96-98.
[14] Diaz GE, Wirrell EC, Matsumoto JY, Krecke KN. Bilateral striopallidodentate calcinosis with paroxysmal kinesigenic dyskinesia[J]. Pediatr Neurol, 2010, 43:46-48.
[15] Chung EJ, Cho GN, Kim SJ. A case of paroxysmal kinesigenic dyskinesia in idiopathic bilateral striopallidodentate calcinosis [J]. Seizure, 2012, 21:802-804.
[16] Yen DJ, Shan DE, Lu SR. Hyperthyroidism presenting as recurrent short paroxysmal kinesigenic dyskinesia [J]. Mov Disord, 1998, 13:361-363.
[17] Thomas R, Behari M, Gaikwad SB, Prasad K. An unusual case of paroxysmal kinesigenic dyskinesia[J]. J Clin Neurosci, 2002, 9:94-97.
[18] Saiki M, Saiki S, Gondo Y, Murata KY, Sakai K, Hirose G. Ictal alteration of 99mTc ECD SPECT imaging in a patient with secondary paroxysmal kinesigenic dyskinesia caused by hyperglycemia[J]. Rinsho Shinkeigaku, 2005, 45:312-316.
[19] Jin D, Yoon WT, Suh BC, Moon HS, Chung PW, Kim YB. Exacerbation of idiopathic paroxysmal kinesigenic dyskinesia in remission state caused by secondary hypoparathyroidism with hypocalcemia after thyroidectomy: evidence for ion channelopathy[J]. Brain Dev, 2012, 34:840-843.
[20] Mir P, Huang YZ, Gilio F, Edwards MJ, Berardelli A, Rothwell JC, Bhatia KP. Abnormal cortical and spinal inhibition in paroxysmal kinesigenic dyskinesia[J]. Brain, 2005, 128(Pt 2): 291-299.
[21] Kang SY, Sohn YH, Kim HS, Lyoo CH, Lee MS. Corticospinal disinhibition in paroxysmal kinesigenic dyskinesia [J]. Clin Neurophysiol, 2006, 117:57-60.
[22] Shin HW, Kang SY, Hallett M, Sohn YH. Extended surround inhibition in idiopathic paroxysmal kinesigenic dyskinesia [J]. Clin Neurophysiol, 2010, 121:1138-1141.
[23] Wei H, Sun Y, Chen H, Wang DQ, Li LP, Ding Y, Liu AH, Lu CF, Wang YP. Somatosensory disinhibition in patients with paroxysmal kinesigenic dyskinesia [J]. Chin Med J (Engl), 2012, 125:838-842.
[24] Luo C, Chen Y, Song W, Chen Q, Gong Q, Shang HF. Altered intrinsic brain activity in patients with paroxysmal kinesigenic dyskinesia by PRRT2 mutation: altered brain activity by PRRT2 mutation[J]. Neurol Sci, 2013, 34:1925-1931.
[25] Hsu WY, Liao KK, Tseng YJ, Kwan SY, Chen RS, Lin YY. Reduced postmovement cortical inhibition in patients with paroxysmal kinesigenic dyskinesia[J]. Neurology, 2013, 81:353-360.
[26] Hsu WY, Kwan SY, Liao KK, Chen RS, Lin YY. Altered inhibitory modulation of somatosensory cortices in paroxysmal kinesigenic dyskinesia[J]. Mov Disord, 2013, 28:1728-1731.
[27] Kim JH, Kim DW, Kim JB, Suh SI, Koh SB. Thalamic involvement in paroxysmal kinesigenic dyskinesia: a combined structural and diffusion tensor MRI analysis [J]. Hum Brain Mapp, 2015, 36:1429-1441.
[28] Ren J, Lei D, Yang T, An D, Xiao F, Li L, Huang X, Gong Q, Zhou D. Increased interhemispheric resting - state functional connectivity in paroxysmal kinesigenic dyskinesia: a resting - state fMRI study[J]. J Neurol Sci, 2015, 351:93-98.
[29] Liu ZR, Miao HH, Yu Y, Ding MP, Liao W. Frequency-specific local synchronization changes in paroxysmal kinesigenic dyskinesia[J]. Medicine (Baltimore), 2016, 95:e3293.
[30] Hsiao FJ, Hsu WY, Chen WT, Chen RS, Lin YY. Abnormal somatosensory synchronization in patients with paroxysmal kinesigenic dyskinesia: a magnetoencephalographic study [J]. Clin EEG Neurosci, 2017, 48:288-294.
[31] Long Z, Xu Q, Miao HH, Yu Y, Ding MP, Chen H, Liu ZR, Liao W. Thalamocortical dysconnectivity in paroxysmal kinesigenic dyskinesia: combining functional magnetic resonance imaging and diffusion tensor imaging[J]. Mov Disord, 2017, 32:592-600.
[32] Zhou HY, Zhan FX, Tian WT, Zhang C, Wang Y, Zhu ZY, Liu XL, Xu YQ, Luan XH, Huang XJ, Chen SD, Cao L. The study of exercise tests in paroxysmal kinesigenic dyskinesia[J]. Clin Neurophysiol, 2018, 129:2435-2441.
[33] Liu YT, Chen YC, Kwan SY, Chou CC, Yu HY, Yen DJ, Liao KK, Chen WT, Lin YY, Chen RS, Jih KY, Lu SF, Wu YT, Wang PS, Hsiao FJ. Aberrant sensory gating of the primary somatosensory cortex contributes to the motor circuit dysfunction in paroxysmal kinesigenic dyskinesia [J]. Front Neurol, 2018, 9:831.
[34] Li HF, Yang L, Yin D, Chen WJ, Liu GL, Ni W, Wang N, Yu W, Wu ZY, Wang Z. Associations between neuroanatomical abnormality and motor symptoms in paroxysmal kinesigenic dyskinesia[J]. Parkinsonism Relat Disord, 2019, 62:134-140.
[35] Zhang Y, Ren J, Qin Y, Yang C, Zhang T, Gong Q, Yang T, Zhou D. Altered topological organization of functional brain networks in drug - naive patients with paroxysmal kinesigenic dyskinesia[J]. J Neurol Sci, 2020, 411:116702.
[36] Li L, Lei D, Suo X, Li X, Yang C, Yang T, Ren J, Chen G, Zhou D, Kemp GJ, Gong Q. Brain structural connectome in relation to PRRT2 mutations in paroxysmal kinesigenic dyskinesia[J]. Hum Brain Mapp, 2020, 41:3855-3866.
[37] Li X, Lei D, Niu R, Li L, Suo X, Li W, Yang C, Yang T, Ren J, Pinaya WHL, Zhou D, Kemp GJ, Gong Q. Disruption of gray matter morphological networks in patients with paroxysmal kinesigenic dyskinesia[J]. Hum Brain Mapp, 2021, 42:398-411.
[38] Ekmen A, Meneret A, Valabregue R, Beranger B, Worbe Y, Lamy JC, Mehdi S, Herve A, Adanyeguh I, Temiz G, Damier P, Gras D, Roubertie A, Piard J, Navarro V, Mutez E, Riant F, Welniarz Q, Vidailhet M, Lehericy S, Meunier S, Gallea C, Roze E. Cerebellum dysfunction in patients with *PRRT2*-related paroxysmal dyskinesia[J]. Neurology, 2022, 98:e1077-1089.
[39] Kim MK, Suh SI, Kim JH. Cerebello - thalamofrontal dysconnectivity in paroxysmal kinesigenic dyskinesia: a resting-state fMRI study[J]. Parkinsonism Relat Disord, 2022, 99:1-7.
[40] Whitty CW, Lishman WA, Fitzgibbon JP. Seizures induced by movement: a form of reflex epilepsy[J]. Lancet, 1964, 2:1403-1406.
[41] Loong SC, Ong YY. Paroxysmal kinesigenic choreoathetosis:

report of a case relieved by L-dopa[J]. J Neurol Neurosurg Psychiatry, 1973, 36:921-924.
[42] Demirkiran M, Jankovic J. Paroxysmal dyskinesias: clinical features and classification[J]. Ann Neurol, 1995, 38:571-579.
[43] Silkis I. The cortico-basal ganglia-thalamocortical circuit with synaptic plasticity. Ⅱ: mechanism of synergistic modulation of thalamic activity via the direct and indirect pathways through the basal ganglia[J]. Biosystems, 2001, 59:7-14.
[44] Chen W, de Hemptinne C, Miller AM, Leibbrand M, Little SJ, Lim DA, Larson PS, Starr PA. Prefrontal - subthalamic hyperdirect pathway modulates movement inhibition in humans [J]. Neuron, 2020, 106:579-588.e3.
[45] Jellinger KA. Neuropathology and pathogenesis of extrapyramidal movement disorders: a critical update. Ⅰ: hypokinetic - rigid movement disorders [J]. J Neural Transm (Vienna), 2019, 126:933-995.
[46] Jellinger KA. Neuropathology and pathogenesis of extrapyramidal movement disorders: a critical update. Ⅱ: hyperkinetic disorders[J]. J Neural Transm (Vienna), 2019, 126: 997-1027.
[47] Zhou B, Chen Q, Gong Q, Tang H, Zhou D. The thalamic ultrastructural abnormalities in paroxysmal kinesigenic choreoathetosis: a diffusion tensor imaging study[J]. J Neurol, 2010, 257:405-409.
[48] Zhou B, Chen Q, Zhang Q, Chen L, Gong Q, Shang H, Tang H, Zhou D. Hyperactive putamen in patients with paroxysmal kinesigenic choreoathetosis: a resting-state functional magnetic resonance imaging study[J]. Mov Disord, 2010, 25:1226-1231.
[49] Du J, Zhu X, Liu J, Tan Y. Paroxysmal kinesigenic dyskinesia secondary to brain calcification with a homozygous MYORG mutation[J]. Mov Disord, 2021, 36:2699-2701.
[50] Murakami M, Horisawa S, Azuma K, Akagawa H, Nonaka T, Kawamata T, Taira T. Case report: long-term suppression of paroxysmal kinesigenic dyskinesia after bilateral thalamotomy [J]. Front Neurol, 2021, 12:789468.
[51] Kim MO, Im JH, Choi CG, Lee MC. Proton MR spectroscopic findings in paroxysmal kinesigenic dyskinesia[J]. Mov Disord, 1998, 13:570-575.
[52] Tanimura A, Pancani T, Lim SAO, Tubert C, Melendez AE, Shen W, Surmeier DJ. Striatal cholinergic interneurons and Parkinson's disease[J]. Eur J Neurosci, 2018, 47:1148-1158.
[53] Crevier-Sorbo G, Rymar VV, Crevier-Sorbo R, Sadikot AF. Thalamostriatal degeneration contributes to dystonia and cholinergic interneuron dysfunction in a mouse model of Huntington's disease[J]. Acta Neuropathol Commun, 2020, 8: 14.
[54] Eskow Jaunarajs KL, Scarduzio M, Ehrlich ME, McMahon LL, Standaert DG. Diverse mechanisms lead to common dysfunction of striatal cholinergic interneurons in distinct genetic mouse models of dystonia[J]. J Neurosci, 2019, 39:7195-7205.
[55] Tan GH, Liu YY, Wang L, Li K, Zhang ZQ, Li HF, Yang ZF, Li Y, Li D, Wu MY, Yu CL, Long JJ, Chen RC, Li LX, Yin LP, Liu JW, Cheng XW, Shen Q, Shu YS, Sakimura K, Liao LJ, Wu ZY, Xiong ZQ. PRRT2 deficiency induces paroxysmal kinesigenic dyskinesia by regulating synaptic transmission in cerebellum[J]. Cell Res, 2018, 28:90-110.
[56] Mo J, Wang B, Zhu X, Wu X, Liu Y. PRRT2 deficiency induces paroxysmal kinesigenic dyskinesia by influencing synaptic function in the primary motor cortex of rats [J]. Neurobiol Dis, 2019, 121:274-285.
[57] Lee MS, Kim WC, Lyoo CH, Lee HJ. Reciprocal inhibition between the forearm muscles in patients with paroxysmal kinesigenic dyskinesia[J]. J Neurol Sci, 1999, 168:57-61.
[58] Calame DJ, Xiao J, Khan MM, Hollingsworth TJ, Xue Y, Person AL, LeDoux MS. Presynaptic PRRT2 deficiency causes cerebellar dysfunction and paroxysmal kinesigenic dyskinesia [J]. Neuroscience, 2020, 448:272-286.
[59] Lu B, Lou SS, Xu RS, Kong DL, Wu RJ, Zhang J, Zhuang L, Wu XM, He JY, Wu ZY, Xiong ZQ. Cerebellar spreading depolarization mediates paroxysmal movement disorder[J]. Cell Rep, 2021, 36:109743.
[60] Binda F, Valente P, Marte A, Baldelli P, Benfenati F. Increased responsiveness at the cerebellar input stage in the PRRT2 knockout model of paroxysmal kinesigenic dyskinesia [J]. Neurobiol Dis, 2021, 152:105275.
[61] Calderon DP, Fremont R, Kraenzlin F, Khodakhah K. The neural substrates of rapid-onset Dystonia-Parkinsonism[J]. Nat Neurosci, 2011, 14:357-365.
[62] Sathyanesan A, Zhou J, Scafidi J, Heck DH, Sillitoe RV, Gallo V. Emerging connections between cerebellar development, behaviour and complex brain disorders[J]. Nat Rev Neurosci, 2019, 20:298-313.
[63] Tian WT, Huang XJ, Liu XL, Shen JY, Liang GL, Zhu CX, Tang WG, Chen SD, Song YY, Cao L. Depression, anxiety, and quality of life in paroxysmal kinesigenic dyskinesia patients[J]. Chin Med J (Engl), 2017, 130:2088-2094.

（收稿日期：2023-02-16）
（本文编辑：柏钰）

·小词典·

中英文对照名词词汇（四）

轻度皮质发育畸形伴少突胶质细胞增生及癫痫
mild malformations of cortical development with oligodendroglial hyperplasia in epilepsy（MOGHE）

氢质子磁共振波谱
hydrogen proton magnetic resonance spectroscopy（^{1}H-MRS）

丘脑底核 subthalamic nucleus（STN）

躯体症状障碍 somatic symptom disorder（SSD）

全基因组测序 whole genome sequencing（WGS）

全面性癫痫 general epilepsy（GE）

全面性惊厥性癫痫持续状态
generalized convulsive status epilepticus（GCSE）

全面性强直-阵挛发作
generalized tonic-clonic seizure（GTCS）

全球疾病负担 Global Burden of Disease（GBD）

全外显子组测序 whole exome sequencing（WES）

缺氧缺血性脑病 hypoxic-ischemic encephalopathy（HIE）

热性惊厥 febrile seizure（FS）

人类疱疹病毒6型 human herpes virus 6（HHV-6）

认知行为治疗 cognitive behavioral therapy（CBT）