·神经肌肉病·

# 拉莫三嗪治疗Becker型先天性肌强直一例并文献复习

钟洁 林金福 张成 钟欣静 陈雪玲 利婧 朱瑜龄

【摘要】 **目的** 报道拉莫三嗪治疗1例Becker型先天性肌强直患者的疗效及安全性。**方法与结果** 17岁男性患者，以四肢肌肉僵硬为首发症状，反复运动后症状减轻，血清肌酸激酶水平正常，基因检测提示存在*CLCN1*基因外显子11 c.1205C>T(p.Ala402Val)及*CLCN1*基因外显子8 c.896T>C(p.Val299Ala)错义突变，确诊为Becker型先天性肌强直；其母为*CLCN1*基因外显子11 c.1205C>T(p.Ala402Val)、其父为*CLCN1*基因外显子8 c.896T>C(p.Val299Ala)错义突变，确诊为Becker型先天性肌强直家系，其中*CLCN1*基因外显子8 c.896T>C突变尚无报道。经拉莫三嗪连续治疗5年后肌强直症状长期缓解，且无任何药物不良反应。**结论** 该例*CLCN1*基因外显子8 c.896T>C错义突变进一步扩展了*CLCN1*基因突变谱。拉莫三嗪治疗效果良好，为Becker型先天性肌强直的治疗提供了新的思路。

【关键词】 先天性肌强直； 三嗪类； 基因； 突变，误义； 系谱

## Treatment of Becker myotonia congenita with lamotrigine: one case report and review of literatures

ZHONG Jie, LIN Jin-fu, ZHANG Cheng, ZHONG Xin-jing, CHEN Xue-ling, LI Jing, ZHU Yu-ling
*Department of Neurology, the First Affiliated Hospital, Sun Yat-sen University, Guangzhou 510080, Guangdong, China*
*Corresponding author: ZHANG Cheng (Email: zhangch6@mail.sysu.edu.cn)*

【**Abstract**】 **Objective** To report the efficacy and safety of lamotrigine in the treatment of one case of Becker myotonia congenita. **Methods and Results** A 17-year-old male had muscle stiffness in the limbs as the first symptom, which could be alleviated after repeated exercise. The creatine kinase (CK) level was normal. Genetic testing showed there were two missense mutations c.1205C>T (p.Ala402Val) and c.896T>C (p.Val299Ala) located in exon 11 and 8 of *CLCN1* gene respectively in the proband. The missense mutation c.1205C>T (p.Ala402Val) in exon 11 was found out in his mother and c.896T>C (p.Val299Ala) located in exon 8 was found out in his father. The latter, exon 8 c.896T>C of *CLCN1* gene has not been reported. The proband was clearly diagnosed as Becker myotonia congenita, and his family was diagnosed as Becker myotonia congenita pedigree. After 5 years´ treatment with lamotrigine, the symptom of myotonia was significantly improved and no adverse reactions was observed. **Conclusions** The missense mutation in exon 8 c.896T>C in this patient further expanded the *CLCN1* gene mutation spectrum. Lamotrigine is effective in treating Becker myotonia congenita, providing a new idea for the treatment of myotonia congenita.

【**Key words**】 Myotonia congenita; Triazines; Genes; Mutation, missense; Pedigree

This study was supported by the National Natural Science Foundation of China (No. 81471280, 81771359), the National Natural Science Foundation for Young Scientists of China (No. 81601087), and

doi:10.3969/j.issn.1672-6731.2019.05.009

基金项目：国家自然科学基金资助项目(项目编号：81471280)；国家自然科学基金资助项目(项目编号：81771359)；国家自然科学基金青年科学基金资助项目(项目编号：81601087)；广东省广州市2015年产学研专项项目(项目编号：1561000153)

作者单位：510080 广州，中山大学附属第一医院神经科[钟洁(现在广西中医药大学第一附属医院脑病科，邮政编码：530023)、钟欣静(现在广西医科大学第六附属医院老年病科，邮政编码：537000)、陈雪玲(现在海南省琼海市人民医院神经内科，邮政编码：571400)]

通讯作者：张成，Email：zhangch6@mail.sysu.edu.cn

2015 Production, Study and Research Special Project of Guangzhou, Guangdong Province, China (No. 1561000153).

**Conflicts of interest:** none declared

先天性肌强直是由位于染色体7q35的氯离子电压门控通道(*CLCN*)基因突变所致,主要以肌强直和肌肉肥大、肢体僵硬、动作笨拙为临床特征;表现为骨骼肌在随意收缩或物理刺激收缩后呈短暂性僵硬状态不能立即放松,而重复收缩后则完全松弛,症状在寒冷环境中加重、温暖环境减轻,肌肉肥大酷似运动员,叩击后可见肌球征。先天性肌强直发病率为(0.3~0.6)/10万[1],根据遗传形式可以分为常染色体显性遗传性Thomsen病和常染色体隐性遗传性Becker病,两种类型均为*CLCN1*基因点突变所致[1]。迄今共报道200余个*CLCN1*基因突变[2],但Becker型先天性肌强直患者十分少见。本文报道1例对拉莫三嗪治疗反应良好的Becker型先天性肌强直患者,拟根据其临床特征、基因突变类型并结合文献资料,对拉莫三嗪的疗效与安全性进行评价,以期为该药治疗Becker型先天性肌强直提供新的临床证据。

## 病例资料

患者 男性,17岁。主因四肢肌肉僵硬3年余并缓慢进展,于2013年12月4日至我院神经科就诊。患者3年前(2010年8月)无明显诱因出现四肢肌肉僵硬,表现为由坐位转为直立位时双下肢肌肉僵硬,约持续3 s后方能起步正常行走或跑步,用力握拳后不易放松,约持续3 s后手指方可伸展;上述症状经反复活动后可有所减轻,天气寒冷时加重。发病期间无用力闭眼后睁眼困难、无复视,无胸闷气短等症状与体征。门诊印象:疑似先天性肌强直、发作性运动诱发性运动障碍(PKD)、强直性肌营养不良症(DM)。患者自发病以来精神、睡眠尚可,大小便无异常。

既往史、个人史及家族史 既往身体健康,生长发育里程碑正常。父母非近亲婚配,身体健康,家族中无类似疾病史。

体格检查 神志清楚,语言流利,认知功能正常,脑神经检查无异常。四肢肌力5级,启动时四肢肌张力增高,活动一段时间后恢复正常;腱反射正常,无肌肉压痛,无肌束颤动;四肢肌肉肥大,以股二头肌肥大最为明显,貌似运动员,叩击肱二头肌和鱼际肌可见肌球征,双手用力握拳后手指伸展十分缓慢,久坐后不能立即站起,行走起步僵硬、缓慢,以最初数步尤甚,之后即行走如常。共济运动和深浅感觉正常,病理反射未引出。

辅助检查 实验室检查:血清肌酸激酶(CK)水平正常,各项血液生化指标检测均于正常值范围。影像学检查:头部CT检查未见异常。电生理学检查:心电图正常。因患者肌肉肥大极为明显,故未行肌电图检查。

基因检测和生物信息学分析 采集患者及其父母外周静脉血2 ml,以第二代高通量测序技术[简称第二代测序技术(NGS)]进行(家系)4000种单基因遗传病基因突变分析。经北京全谱医学检验所有限公司检测,证实患者同时存在*CLCN1*基因外显子11 c.1205C>T(p.Ala402Val)和*CLCN1*基因外显子8 c.896T>C(p.Val299Ala)错义突变;其母为*CLCN1*基因外显子11 c.1205C>T(p.Ala402Val)错义突变,其父存在*CLCN1*基因外显子8 c.896T>C(p.Val299Ala)错义突变(图1)。生物信息学分析结果显示,*CLCN1*基因c.1205C>T在千人基因组数据库(http://www.internationalgenome.org/)分布率为0.0024,在千人南方数据库分布率为0.0048,属于罕见变异,生物学危害性较高,为致病性突变;而*CLCN1*基因外显子8 c.896T>C错义突变在dbSNP数据库(http://www.ncbi.nlm.nih.gov/SNP/)、ExAC数据库(http://exac.broadinstitute.org/)、千人基因组数据库,以及千人南方和千人北方数据库均未被收录,为国内外首次报道,生物学提示可能有害。结合患者临床表现、实验室和基因检测结果,且其父母无相关临床表现,符合隐性遗传规律,最终确诊为Becker型先天性肌强直,其家系确定为Becker型先天性肌强直家系(图2)。

治疗与随访 该例患者自首诊日(2013年12月4日)开始即接受抗癫痫药物(AEDs)卡马西平治疗,剂量为100 mg/次(2次/d)口服。规律服药1个月后肌强直症状无明显改善,遂改为拉莫三嗪50 mg/次(2次/d)口服;连续治疗2个月后(2014年3月)四肢

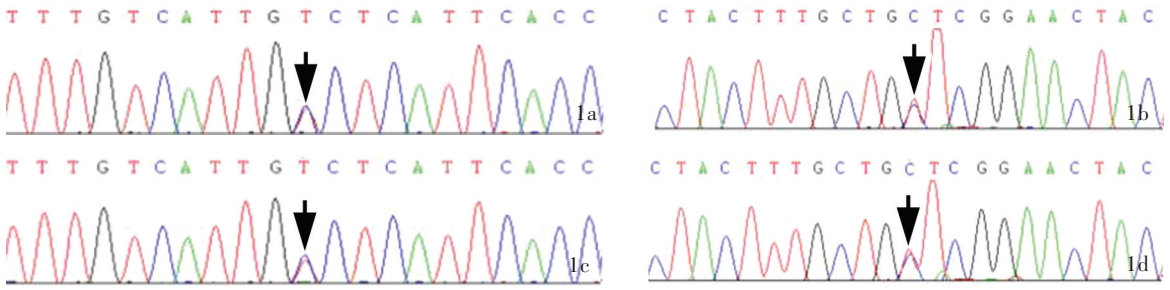


**图1** 基因检测结果可见 1a 患者存在*CLCN1*基因外显子11 c.1205C>T(p.Ala402Val)错义突变(箭头所示) 1b 患者存在*CLCN1*基因外显子8 c.896T>C(p.Val299Ala)错义突变(箭头所示) 1c 患者之母存在*CLCN1*基因外显子11 c.1205C>T(p.Ala402Val)错义突变(箭头所示) 1d 患者之父存在*CLCN1*基因外显子8 c.896T>C(p.Val299Ala)错义突变(箭头所示)

**Figure 1** Genetic testing findings The patient had missense mutation in exon 11 c.1205C>T (p.Ala402Val) of *CLCN1* gene (arrow indicates, Panel 1a). The patient had missense mutation in exon 8 c.896T>C (p.Val299Ala) of *CLCN1* gene (arrow indicates, Panel 1b). His mother had missense mutation in exon 11 c.1205C>T (p.Ala402Val) of *CLCN1* gene (arrow indicates, Panel 1c). His father had missense mutation in exon 8 c.896T>C (p.Val299Ala) of *CLCN1* gene (arrow indicates, Panel 1d).

肌肉僵硬症状有所缓解,且无其他不适。继续服用拉莫三嗪3个月(2014年6月)后肌肉僵硬症状明显改善,握拳、行走无异常,能够游泳。其后,因自行停药2 d症状加重,于2014年7月再度复诊,体格检查握拳后可松开,但由坐位转直立位并行走时需停滞约1 s,未用药。1个月后(2014年8月)复诊,症状继续加重,握拳后虽可松开,但由坐位转直立位并行走停滞时间延长至2 s,且上楼时全身肌肉僵硬、咬牙后不易放松,重新予拉莫三嗪50 mg/次(2次/d)口服;连续治疗1个月后(2014年9月)肌肉僵硬症状有所缓解,握拳后可即刻松开,体位转换停滞时间缩短至1 s,咬牙后较前易松开,叩击性肌强直持续时间缩短为1 s。期间由于患者自行停药2次而致症状再度复发,恢复服药后3 d自觉症状改善。自2015年起始终坚持服药,每3个月复诊1次,症状逐渐改善,1年后(2016年)能够胜任厨师工作。至2018年11月复诊时四肢和面部肌强直症状基本缓解,叩击性肌强直消失。患者服用拉莫三嗪5年余,无其他不适,未曾发生该药常见的皮疹、头痛、视物模糊、恶心呕吐、腹痛腹泻等皮肤、神经系统、消化系统等不良反应。

## 讨 论

根据遗传方式,先天性肌强直可分为常染色体显性遗传性Thomsen病和常染色体隐性遗传性Becker病。Thomsen病多自婴儿期或儿童期发病,表现为用力闭眼不易睁开,轻至中度肌强直和肌肉肥大,寒冷、疲劳、饥饿、情绪激动、月经、妊娠等情况下病情加重,多次反复运动后症状可减轻,即"热身现象",尚可见叩击性肌强直表现。Thomsen病患者表现的肌强直和肌肉肥大多呈普遍性强直和肥大,酷似运动员。Becker病发病较Thomsen病更为隐匿,首发症状出现的较晚,多于青少年期才发病,但肌强直症状较为严重,呈中至重度肌强直伴短暂性肌无力,一般于下肢肌肉开始,逐渐上升,肌无力症状每次发作可持续数秒至数分钟,部分患者可表现为逐渐加重的肌无力和肌萎缩,15%的患者可伴肌肉疼痛[3]。本文家系中的先证者13岁才隐匿发病,以下肢肌强直、肌肉肥大症状首发,相继发展至躯干、上肢,呈典型的肌强直及肌肉肥大,存在"热身现象"和叩击性肌强直,病程中未见呼吸肌、尿道括约肌受累,亦无其他系统损害表现,符合先天性肌强直的特征性临床症状与体征。该病需与先天性副肌强直、发作性运动诱发性运动障碍等离子通道病相鉴别,前者表现为反复运动后肌强直症状加重,故不支持诊断;后者多于青少年期发病,以突发性动作诱发的肌张力障碍为特征,但该例患者卡马西平治疗效果欠佳。先天性肌强直患者血清肌酸激酶水平和心电图检查多无异常,肌电图可见肌强直表现。有研究显示,频率为3 Hz的重复神经电刺激患者耐受性良好且敏感性较高,适用于先天性肌强直基因型-临床表型的相关研究[4]。因该例患者的临床表现十分典型,根据病史、症状与体征即可明确临床诊断,故直接进行基因检测以明确其突变位点,而未行肌电图检测。

先天性肌强直是*CLCN1*基因突变所致,该基因

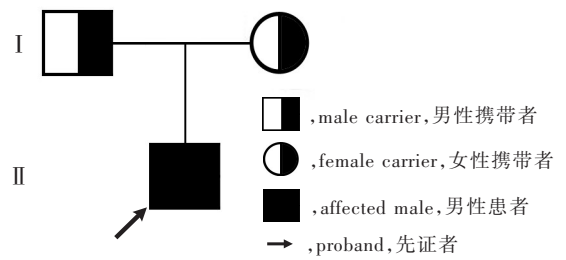


**图2**　Becker型先天性肌强直家系图

**Figure 2**　The pedigree of Becker myotonia congenita.

突变可引起氯离子通道蛋白功能失活，使氯离子内流减少、膜静息电位变化，导致肌细胞兴奋性增高，从而诱发肌强直。*CLCN1*基因包含23个外显子，编码988个氨基酸，组成骨骼肌CLCN1蛋白，为一种跨膜蛋白，当相应基因突变时即可引起该蛋白的主要疏水区氨基酸改变。目前已发现*CLCN1*基因有200余种突变类型，包括缺失、插入、移码、错义及无义突变等。本文患者*CLCN1*基因检测提示存在两种错义突变，其中*CLCN1*基因外显子11 c.1205C>T突变来自母亲，其母表现为杂合突变、其父为野生型；而*CLCN1*基因外显子8 c.896T>C错义突变来自父亲，其父呈杂合突变，母亲为野生型，父母临床表型均正常，由此可以确定患者为常染色体隐性遗传性肌强直。生物信息学分析结果表明，*CLCN1*基因外显子11 c.1205C>T在千人基因组数据库中的分布率为0.0024，属于罕见变异，生物学危害性较高，且已被Fialho等[5]报告为致病性突变；另一个是*CLCN1*基因外显子8 c.896T>C错义突变，该突变在数据库中未收录，生物信息学提示可能有害，Fialho等[5]报告与c.896T>C突变相近的c.895G>C(p.Val299Leu)为致病性突变。因此，该例患者*CLCN1*基因外显子8 c.896T>C错义突变进一步扩展了*CLCN1*基因突变谱。

目前临床上治疗先天性肌强直的药物主要是卡马西平和美西律。卡马西平和美西律均为钠通道阻断剂，通过防止因细胞膜过度去极化导致的传导阻滞，减轻骨骼肌持续性自发收缩后产生的短暂性动作电位抑制，以减轻肌强直[6]，但这两种药物的临床疗效均不十分理想。拉莫三嗪是英国Wellcome实验室在1978年的一项实验研究中的意外发现，1985年该实验室的研究表明，拉莫三嗪对强直发作的控制效果优于苯妥英钠和苯巴比妥等当时的主流抗癫痫药物。1990年，拉莫三嗪首先在爱尔兰上市，1992年，美国食品与药品管理局(FDA)批准其用于治疗部分性发作。2005年，该药在我国上市，主要用于12岁以上儿童及成人的部分性发作和全面性强直-阵挛发作(GTCS)的单药以及2岁以上儿童或成人的添加治疗，其半衰期为24~30小时，每天可服用2次。2019年新研发的拉莫三嗪分散片剂已获得国家食品药品监督管理总局(CFDA)批准上市，用于治疗2岁以上人群的癫痫发作，相较之前的普通片剂而言，新的剂型更适用于全年龄段患者。作为新型广谱抗癫痫药物，拉莫三嗪因不良反应少、药物相互作用少等特点而被广泛应用于临床。拉莫三嗪为苯三嗪衍生物，其作用机制是通过阻断神经元表面电压门控性钠离子通道(VGSC)而稳定细胞膜，抑制神经元细胞异常放电；稳定突触前膜，抑制兴奋性神经递质，尤其是谷氨酸的释放；与此同时，还具有阻断电压门控性钙离子通道(VGCC)的作用[7]。2017年，Andersen等[8]开展的一项随机双盲对照临床研究结果显示，与传统抗心律失常药物美西律相比，拉莫三嗪对缓解肌强直更为有效，其药理学机制即与阻断神经元表面电压门控性钠离子通道、抑制兴奋性神经递质有关。Skov等[9]发现，拉莫三嗪与卢非酰胺联合应用的疗效更为显著，目前尚无相关临床疗效和长期随访报道。本文患者自17岁开始服用拉莫三嗪，单药治疗5年余，肌强直症状明显缓解，与国外文献报道的结果相一致[8-9]。患者治疗期间曾因自行停药导致病情反复，重新服药后3天肌强直症状即获得改善，且治疗期间未出现任何药物不良反应[10]。

综上所述，本文患者*CLCN1*基因外显子8 c.896T>C错义突变进一步扩展了*CLCN1*基因突变谱。同时该例患者亦是国内首次应用拉莫三嗪治疗Becker型先天性肌强直的病例，经过5年多的随访，疗效显著，肌强直症状改善明显。下一步我们将进一步扩大样本量加以分析，并对其药理学机制进行深入研究。

**利益冲突**　无

## 参　考　文　献

[1] Wu J, Jia JP. Neurology[M]. 3rd ed. Beijing: People's Medical Publishing House, 2015: 439-440.[吴江, 贾建平. 神经病学[M]. 3版. 北京: 人民卫生出版社, 2015: 439-440.]

[2] Portaro S, Altamura C, Licata N, Camerino GM, Imbrici P, Musumeci O, Rodolico C, Conte Camerino D, Toscano A, Desaphy JF. Clinical, molecular, and functional characterization of CLCN1 mutations in three families with recessive myotonia

congenita[J]. Neuromolecular Med, 2015, 17:285-296.
[3] Feng XH, Cui LY. Progress in skeletal muscle channelopathies [J]. Zhongguo Shi Yong Nei Ke Za Zhi, 2011, 31:84-85.[冯新红, 崔丽英. 骨骼肌离子通道病研究现状和进展[J]. 中国实用内科杂志, 2011, 31:84-85.]
[4] Modoni A, D'Amico A, Dallapiccola B, Mereu ML, Merlini L, Pagliarani S, Pisaneschi E, Silvestri G, Torrente I, Valente EM, Lo Monaco M. Low-rate repetitive nerve stimulation protocol in an Italian cohort of patients affected by recessive myotonia congenita[J]. J Clin Neurophysiol, 2011, 28:39-44.
[5] Fialho D, Schorge S, Pucovska U, Davies NP, Labrum R, Haworth A, Stanley E, Sud R, Wakeling W, Davis MB, Kullmann DM, Hanna MG. Chloride channel myotonia: exon 8 hot-spot for dominant-negative interactions[J]. Brain, 2007, 130: 3265-3274.
[6] Ginanneschi F, Mignarri A, Lucchiari S, Ulzi G, Comi GP, Rossi A, Dotti MT. Neuromuscular excitability changes produced by sustained voluntary contraction and response to mexiletinein myotonia congenita[J]. Neurophysiol Clin, 2017, 47:247-252.
[7] Lin N, Liu Y, Qi H, Zhou FL, Xin Q, Wang HY. The effect of lamotrigine on anti-depressant of and its mechanism[J]. Jining Yi Xue Yuan Xue Bao, 2018, 41:163-166.[林娜, 柳洋, 祁晖, 周凤玲, 辛勤, 王海英. 拉莫三嗪抗抑郁作用及其机制研究[J]. 济宁医学院学报, 2018, 41:163-166.]
[8] Andersen G, Hedermann G, Witting N, Duno M, Andersen H, Vissing J. The antimyotonic effect of lamotrigine in non-dystrophic myotonias: a double-blind randomized study[J]. Brain, 2017, 140:2295-2305.
[9] Skov M, de Paoli FV, Nielsen OB, Pedersen TH. The anti-convulsants lacosamide, lamotrigine, and rufinamide reduce myotonia in isolated human and rat skeletal muscle[J]. Muscle Nerve, 2017, 56:136-142.
[10] Lan L, Shan P, Li CJ. Review of recent literatures on adverse reactions of lamotriazine[J]. Zhongguo Yao Wu Lan Yong Fang Zhi Za Zhi, 2016, 22:108-109.[蓝兰, 单萍, 李成建. 拉莫三嗪不良反应近况文献概述[J]. 中国药物滥用防治杂志, 2016, 22:108-109.]

（收稿日期:2019-04-23）

## ASNO 2019 Annual Meeting

Time: September 26–29, 2019

Venue: HNBK International Convention Center, Taipei, Taiwan, China

Website: https://asno2019.tw/

Asian Society of Neuro-Oncology (ASNO) 2019 Annual Meeting will take place in HNBK International Convention Center, Taipei, Taiwan, China on September 26–29, 2019. ASNO invites neurosurgeons, neuro-oncologists, and researchers from around the world to submit abstracts for presentation at this meeting.

The theme of this meeting is "Advances in Neuro-oncology and Clinical Treatments", including the following categories: clinical research of brain tumor (including surgery/medical treatment/radiation/clinical trial/pathology); basic research of brain tumor (including experimental/immune/medical engineering/AI); nursing/paramedical care/secondary data analysis; spinal tumor; pediatric tumor.

The meeting will feature talks from invited speakers as well as talks selected from submitted abstracts, a poster session, and also activities to promote discussion and interaction between the participants. The topics will include brain tumor, spinal tumor, medical neuro-oncology, nursing research in neuro-oncology, and socioeconomic impact of CNS tumors. Abstracts will be peer reviewed. Acceptance will be based on content, available space, and overall program balance.

Furthermore, to improve the academic level of ASNO 2019 and to rapidly distribute the most updated researches, the ASNO 2019 organizing committee will work with Journal of Neuro-oncology (JNO) to enhance the visibility of Asian academic works. The ASNO 2019 organizing committee and JNO will jointly select 12 to 15 articles from the submitted abstracts, and publish them in a JNO special issue after completion of manuscript submission and peer review. The JNO will offer an Outstanding Paper Award for the best original paper published in this issue. This project is supported by Jason P. Sheehan, who is chief editor of JNO.

It is our aim that this supplementary issue will be published in the spring of 2020. This issue will cover not only the most advanced surgical techniques but also the radiation oncology, medical oncology, laboratory science studies in the neuro-oncology field. Most importantly, this will be an issue rich in Asian-specific neuro-oncological problems and treatment strategy uniquely suited for Asian races.