·病例报告·

脊髓小脑性共济失调2型一家系

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【关键词】 脊髓小脑共济失调；　三核苷酸重复扩增；　系谱；　病例报告

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A pedigree of spinocerebellar ataxia type 2

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患者　男性，20岁。主因持物、行走不稳4年，于2017年7月25日入院。患者4年前无明显诱因出现行走不稳、双下肢无力，表现为上下楼梯或蹲起稍困难，上述症状与体征呈进行性加重，但无跌倒，无吟诗样语言或言语不清，无吞咽困难，遂以“遗传性小脑性共济失调”收入院。患者自发病以来，精神、睡眠、饮食尚可，大小便正常，体重无明显增减。既往身体健康，无外伤史及手术史，无食物与药物过敏史，无疫区接触史，无传染性疾病病史，无烟酒嗜好。父母身体健康，否认近亲婚配；外祖母、二姨母和四姨母均有类似行走不稳病史，外祖母于52岁发病、65岁死亡，二姨母43岁发病、55岁死亡，四姨母于39岁发病、目前已患病4年，不能行走，其余亲属无类似病史。入院后体格检查：神志清楚，构音正常，双眼各向活动正常，可见水平性眼震，双侧鼻唇沟对称，伸舌居中，无纤颤，无吞咽困难；四肢肌力正常、肌张力降低，腱反射减弱，双侧指鼻试验、跟-膝-胫试验均欠稳准；Romberg征睁、闭眼失稳，行走呈宽基底步态；深浅感觉正常；脑膜刺激征阴性，双侧Babinski征阴性。实验室检查：血清学检查各项指标均于正常值范围。影像学检查：头部MRI显示，双侧大脑半球结构对称，灰白质对比正常，小脑半球萎缩，脑沟增宽，脑干呈轻度萎缩，脑桥小脑三角、小脑延髓池及桥前池增宽，第四脑室略扩大；其余脑室、脑池、脑裂及脑沟对称，大小、形态正常，中线结构居中（图1），符合橄榄体脑桥小脑萎缩的MRI表现。基因检测：根据上述临床表现和影像学检查，可疑脊髓小脑性共济失调（SCA）。为进一步证实临床诊断及其分型，经患者及其父母签署知情同意书后分别对临床常见的8种类型脊髓小脑性共济失调（SCA1、SCA2、SCA3、SCA6、SCA7、SCA8、SCA12、SCA17型）所对应基因（*ATXN1*、*ATXN2*、*ATXN3*、*CACNA1A*、*ATXN7*、*ATXN8*、*PPP2R2B*、*TBP*）的胞嘧啶-腺嘌呤-鸟嘌呤（CAG）拷贝数进行检测。结果显示，患者（先证者）*ATXN2*基因CAG拷贝数为45次（14～28次），呈异常扩增（图2）；其SCA1、SCA3、SCA6、SCA7、SCA8、SCA12、SCA17型基因位点所对应基因（*ATXN1*、*ATXN3*、*CACNA1A*、*ATXN7*、*ATXN8*、*PPP2R2B*、*TBP*）的CAG

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李燕新与宋莉对本文有同等贡献

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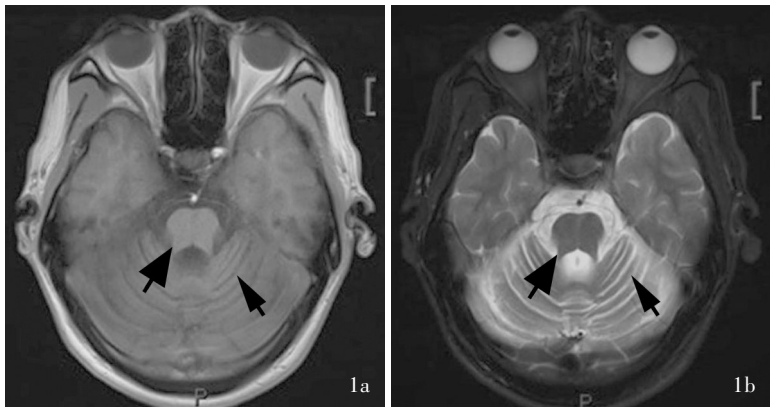

图1 头部MRI检查可见小脑萎缩(细箭头所示),脑干轻度萎缩(粗箭头所示) 1a 横断面T_1WI扫描 1b 横断面T_2WI扫描

Figure 1 Brain MRI showed cerebellar atrophy (thin arrows indicate) and mild atrophy of brain stem (thick arrows indicate). Axial T_1WI (Panel 1a). Axial T_2WI (Panel 1b).

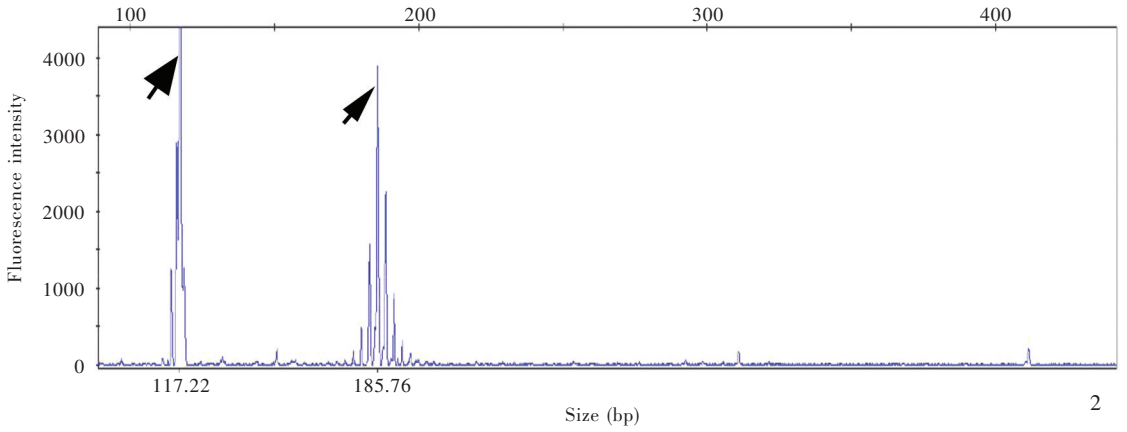

图2 先证者*ATXN2*基因CAG扩增区域片段长度(45次拷贝)分别为117 bp(粗箭头所示)和186 bp(细箭头所示)

Figure 2 The size of CAG expansion in *ATXN2* gene of proband (45 repeats) is 117 bp (thick arrow indicates) and 186 bp (thin arrow indicates) respectively.

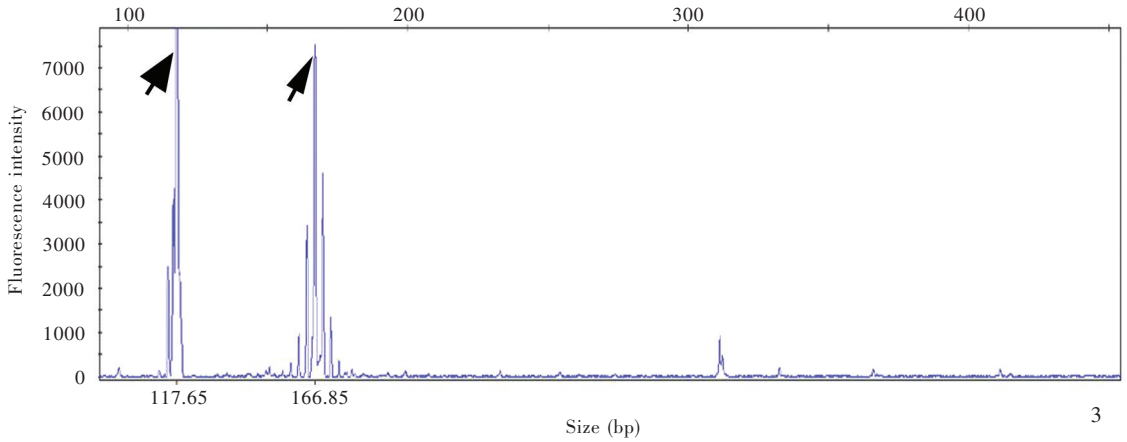

图3 先证者之母*ATXN2*基因CAG扩增区域片段长度(39次拷贝)分别为118 bp(粗箭头所示)和167 bp(细箭头所示)

Figure 3 The size of CAG expansion in the *ATXN2* gene of proband's mother (39 repeats) is 118 bp (thick arrow indicates) and 167 bp (thin arrow indicates) respectively.

拷贝数则均于正常范围内。其母*ATXN2*基因CAG拷贝数为39次,超出正常范围(图3);其父*ATXN2*基因CAG拷贝数为23次,于正常范围内。根据基因检测结果,结合患者临床表现、影像学所见及家族史,明确诊断为SCA2型,该家系为SCA2型家系(图4)。患者共住院5 d,入院后分别予以骨骼肌松弛药巴氯芬1.67 mg/次(3次/d,每隔3天增服5 mg/d)、抗震颤麻痹药苯海索1 mg/次(3次/d)口服对症治疗,

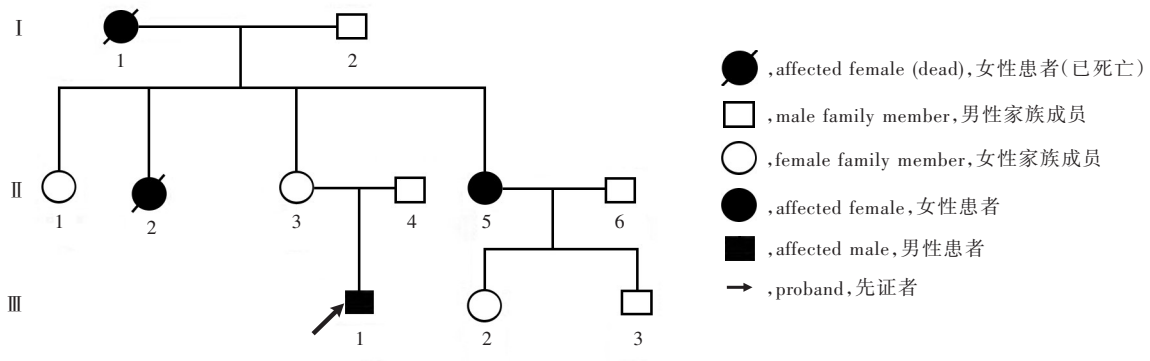

图4　SCA2型家系图

Figure 4　Pedigree of SCA2 family.

出院时症状未见明显缓解，继续服药。出院2周后门诊复查，巴氯芬维持10 mg/次(3次/d)口服治疗，6个月后随访时症状未见明显加重。

讨　论

脊髓小脑性共济失调是一类由遗传因素引起的、以进行性平衡和协调障碍为特征的迟发型神经系统遗传性疾病，占神经系统遗传性疾病的10%～15%[1-3]。该病具有高度的临床异质性，根据其临床表现、基因学三核苷酸重复序列特点及其生物化学改变等可分为SCA1～SCA40型及齿状核红核苍白球路易体萎缩(DRPLA)等亚型，各亚型之间症状既有重叠又各有特征，单从临床表现无法加以鉴别，唯有基因检测是最为有效的诊断与鉴别诊断方法。SCA2型的临床表现主要包括共济失调、肢体震颤、腱反射减弱，构音、眼球运动以及认知功能障碍等[4-6]，病理学呈广泛性大脑、小脑、脑干受累，是由*ATXN2*基因(定位于染色体12q23～24.1)CAG拷贝所致，一般拷贝数＞33次。对于SCA2型的发病机制尚不十分明确，亦缺乏有效的治疗手段，主要是以对症、支持治疗来提高患者的生活质量[7-8]。自1861年Menzel首次报告高加索地区的脊髓小脑性共济失调一家系以来，世界各地陆续出现关于脊髓小脑性共济失调家系或不同亚型的病例报道[9-13]，而我国鲜见SCA2型的报道。SCA2型为小脑及小脑外结构(包括脑桥、基底节、大脑皮质等)的慢性进行性退变，属于常染色体显性遗传，是神经系统遗传性疾病中最为严重的疾病之一[14]。目前认为，SCA2型是由*ATXN2*基因CAG拷贝数异常扩增导致其编码的蛋白质中多聚谷氨酰胺异常延伸扩展而产生致病蛋白Ataxin-2所致，Ataxin-2蛋白主要聚集在小脑等部位的神经元胞核内，形成核内包涵体，如果部分致病蛋白Ataxin-2出现在胞质中，则可导致SCA2型，此即SCA2型的分子病理学机制[15-16]。SCA2型以橄榄体脑桥小脑萎缩为病理学特征，其小脑皮质浦肯野细胞和树突状细胞的部分缺失导致小脑皮质分子层突触消失，进而引起小脑萎缩[16-17]，此与本文患者的头部MRI表现相吻合。我国首例SCA2型病例由唐北沙等[18]于1997年报告，此型患者大多于30～40岁发病，存在遗传早现现象[19]，可在连续数代中出现显性遗传性疾病，不仅发病年龄提前且病情严重程度增加。本文家系即存在遗传早现现象，先证者16岁发病，而其外祖母52岁发病、二姨母43岁发病、四姨母39岁发病。王康和王国相[20]报告的我国SCA2型患者*ATXN2*基因CAG拷贝数为37～56次，Fernandez等[21]报告1例68岁晚发型SCA2型患者的*ATXN2*基因CAG拷贝数为33次。本文先证者及其母*ATXN2*基因CAG拷贝数分别为45和39次，均属异常，但其母目前仍未发病，可能与以下原因有关：(1)据Sobczak和Krzyzosiak[22]报告，凡CAG拷贝数中存在插入的胞嘧啶-腺嘌呤-腺嘌呤(CAA)片段者发病年龄相对较晚，而临床症状与体征相对较轻，先证者之母CAG拷贝数中可能存在CAA片段的插入，因此临床表现不明显。(2)有研究发现，SCA2型发病年龄与CAG拷贝数呈正相关关系($R^2=0.620$，$P<0.0001$)；且发病年龄越晚，临床症状越轻、病程越长、病情进展越缓慢，先证者之母CAG拷贝数相对少，可能尚未出现临床症状[23-24]。(3)先证者之母CAG拷贝数异常扩增导致编码的多聚谷氨酰胺产生的致病蛋白可

能仅出现在神经元胞核内，还未分布到胞质发挥作用。(4)可能与遗传修饰有关。多聚谷氨酰胺产生的致病蛋白可通过非共价“极性拉链”或转谷氨酰胺酶介导的共价交联与细胞特异性因子相互作用产生复合物，从而影响致病蛋白Ataxin-2的功能。(5)临床异质性的影响，由于环境、机体等各方面的影响，SCA2型患者的临床表现不尽相同。(6)个体差异性，先证者之母至今尚未发病，可能与其免疫机制无明显缺陷有关，故未出现明显症状与体征，尚需进一步随访。

本文报告的SCA2型一家系中，先证者*ATXN2*基因CAG拷贝数呈异常扩增(45次)，并且符合SCA2型的临床表现；先证者之母CAG拷贝数39次，超出正常范围，但尚未发病。SCA2型的临床表现复杂，其症状与体征的异质性和不普遍性是明确诊断的主要障碍，除小脑性共济失调症状外，因脊髓、脑干、基底节等部位神经元变性所致的其他特征也同时存在，因此不可能仅凭临床症状与体征明确临床分型，基因检测是诊断与鉴别诊断的唯一方法。

利益冲突 无

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WFNS Congress Beijing 2019

Time: September 9–12, 2019

Venue: Beijing, China

Website: http://www.wfns2019.org/

The WFNS Congress Beijing 2019 will be held on September 9–12, 2019 in Beijing, China under the auspices of the World Federation of Neurosurgical Societies (WFNS), which is hosted by the Chinese Medical Doctor Association and Chinese Medical Association.

Founded in 1955, The WFNS is a professional and scientific non-governmental organization comprised of 130 members including 5 continental associations, 119 national or regional neurosurgical societies and 6 affiliate societies. WFNS is the highest academic organization of neurosurgery and the family of all neurosurgeons around the world. The WFNS Congress plays an important role in enhancing medical technology, strengthening academic exchanges and promoting collaborative research and exploration in neurosurgery and related disciplines.

"Glorious Neurosurgery" is the theme of WFNS Congress Beijing 2019. We will hold the opening ceremony on the Great Wall in the golden season. The conference hall is adjacent to the "Bird´s Nest", the main venue of the 2008 Summer Olympics and the 2022 Winter Olympics. Apart from a perfect scientific program, we will work hard to organize a wealth of cultural activities and very interesting tours for you and your companions. We will also invite 150 young neurosurgeons from the developing countries especially along the "Belt and Road" regions to attend the congress free of registration fee, food and accommodation. Furthermore, we will provide international return fares and a month-long clinical training afterwards in Beijing to 50 of them free of charge in food and accommodation.

Fifth European Stroke Organization Conference

Time: May 22–24, 2019

Venue: Milan, Italy

Website: http://eso-conference.org/2019/

The 5th European Stroke Organization Conference (ESOC) will take place in Milan, Italy, on May 22–24, 2019. ESOC 2019 will build on the enormous success of the last four European Stroke Organization (ESO) Conferences. ESOC is Europe´s leading forum for discussing and disseminating the latest advances in stroke care.

Over 1800 abstracts were submitted to ESOC 2018 in Gothenburg. In the large clinical trials sessions, results from 10 major randomized controlled trials (RCTs) were presented, many of which with accompanying high impact publications. Our delegate numbers continue to grow year on year and we are confident ESOC 2019 will be the largest yet.

One of the highlights of ESOC 2018 was the presentation of the "European Action Plan 2018–2030" which builds on the experience and the format of the previous Helsingborg Declarations. This document was written by ESO in cooperation with the patient organization Stroke Alliance for Europe (SAFE), with the involvement of the World Health Organization (WHO).

ESOC 2019 will see presentations of major clinical trials, state-of-the-art talks by renowned clinicians and researchers and receive updates on the latest guidelines. We will be joined by the Italian Stroke Organization.