Smith-Magenis综合征诊断方法探讨

陈丹纯，唐本玉，潘思年，朱顺叶
（中山大学附属第三医院儿科，广东 广州 510630）

摘　要：【目的】探讨Smith-Magenis综合征的诊断方法及患儿的临床特征，以期提高国内对该病的认识。【方法】本研究通过对患儿行外周血染色体微阵列分析、血尿常规、生长激素激发试验、胰岛素样生长因子-1、胰岛素样生长因子结合蛋白3、皮质醇(8a)、泌乳素、促肾上腺皮质激素、甲状腺功能、肝肾功能、血生化、空腹胰岛素及餐后2 h血糖、乙肝两对半等实验室检查，以及骨龄测定和垂体核磁共振等影像学检查来诊断Smith-Magenis综合征，并对该病患儿的病情进行评估及观察。【结果】该病例中患儿染色体微阵列分析示：chr17p11.2区域发生约3.6 Mb片段缺失，包含RAI1等重要功能基因，该基因与Smith-Magenis综合征相关。结合患儿临床表现，明确诊断患儿为Smith-Magenis综合征。【结论】基因检查是诊断Smith-Magenis综合征的重要标准。儿童特殊面容合并多系统障碍，早期进行基因检查有利于早期诊断，降低时间及经济成本。

关键词：Smith-Magenis综合征；矮小；痛觉不敏感；精神运动发育迟滞；睡眠障碍
中图分类号：R72　　**文献标志码**：A　　**文章编号**：1672-3554(2018)03-0477-04

Research on the Diagnosis of Smith-Magenis Syndrome

CHEN Dan-chun, TANG Ben-yu, PAN Si-nian, ZHU Shun-ye
(Department of Pediatrics, The Third Affiliated Hospital of Sun Yat-Sen University, Guangzhou 510630, China)
Coresponding to: ZHU Shun-ye, E-mail: zhushunye1975@126.com

Abstract: 【Objective】 We explore the diagnosis of Smith-Magenis syndrome and its clinical features of children, to raise the domestic awareness of this disease. 【Methods】 In this study, the child received peripheral blood chromosome microarray analysis, blood routine and urine routine, growth hormone provocation test, insulin-like growth factor I and insulin-like growth factor binding protein Ⅲ test, cortisol (8a) test, prolactin test, adrenocorticotropic hormone test, thyroid function test, liver and kidney function test, blood biochemistry test, fasting insulin test, 2-hour plasma glucose test, the antibodies and antigens test of hepatitis B.The bone age measurement and the pituitary gland MRI were also performed.We use the above figures to diagnose Smith-Magenis syndrome, assess and observe the condition of the child in Smith-Magenis syndrome. 【Results】 In this case, the chromosomal microarray analysis revealed a deletion of about 3.6Mb fragments in the chr17p11.2 region, including main functional gene RAI1, which was associated with Smith-Magenis syndrome. According to the clinical manifestations and the result of chromosome microarray analysis, the diagnosis of children with Smith-Magenis syndrome was made clear. 【Conclusion】 Genetic tests are the standard for diagnosing Smith-Magenis syndrome. When children have special facial features combined with multiple system disorders, early genetic examination is conducive to early diagnosis, and can reduce the time and economic cost.

Key words: Smith-Magenis syndrome; short; pain insensitivity; mental and movement retardation; sleep disorder
[J SUN Yat-sen Univ(Med Sci), 2018, 39(3): 477-480; COV 3]

史密斯-马吉利综合征(Smith-Magenis syndrome, SMS)是一种痛觉不敏感[1]、罕见且复杂的基因疾病。该病于20世纪80年代在美国首次被发现，发病率约为1/25 000[1]，但实际的发病率接

收稿日期：2017-11-27
作者简介：陈丹纯，硕士，研究方向：儿科学，E-mail：chendch7@mail2.sysu.edu.cn；朱顺叶，通信作者，副主任医师，E-mail：zhushunye1975@126.com

近1/15 000[2],主要依靠分子遗传学检查来确诊[3]。截至目前的研究认为,该基因病主要有两种突变可能,一是由于染色体17p11.2区域某一小片段的缺失引起视黄素诱导-1(RAI1)基因的缺失(比例大约为90%[4]),二是RAI1基因自身的突变[5-6]。此外,该片段缺失引起与自身免疫或恶性肿瘤相关的其他基因的突变,从而引起SMS某些症状的可能性不能排除[7]。RAI1间接或直接的突变为SMS致病的关键,临床表现主要为多种神经发育延迟与障碍[8]、睡眠-觉醒障碍[9]、感觉障碍、心理、行为及情绪障碍等,具体为:生长发育迟缓、认知障碍、随年龄增大而愈发明显的独特的面部体征[5]、易觉醒、智力缺陷等[1],另有易怒、强迫行为、多动症、语言障碍、自闭、自虐倾向[10]等心理及行为表现。王莹洁等[11]总结患该病的26例患儿发现,Smith-Magenis综合征患者与Down综合征患儿特征性面容相似,但前者有凸颌及上唇外翻等特异表现,可与后者区别;而手部包括短粗等异常是Smith-Magenis综合征的特征性改变。也有文献[12]指出,Smith-Magenis综合征RAI1基因突变,可引起脂质代谢紊乱,从而出现肥胖。此病仅能对症治疗,如使用褪黑素可改善睡眠障碍[2],功能康复锻炼等,而无有效根治方法。虽然目前国外报道的案例上百例,但国内相关的文献仍比较匮乏。为此,我们就此进行分享,以期提高国内对该病的认识。

1 材料与方法

1.1 病例一般情况

患儿,女,12岁7月,因"自幼较同龄人矮小,伴语言障碍"就诊。患儿系G2P2(第二胎第二产),足月剖宫产,出生体质量2 500 g。现就读小学5年级,不会写字,但认识大部分字,上课期间经常有强迫行为,如反复折叠纸巾,课程分数基本均为"0"分。只可进行简单问答,听简单指令作出动作,认知能力明显低于同龄人,至今仍有遗尿行为。情绪起伏大,曾有自虐倾向;对痛、热不敏感,经常在炎夏于路上赤脚行走。夜间难以入睡,且有易早醒等睡眠障碍表现。父母非近亲结婚,有一胞兄,体健,未表现出类似病史,家族中无遗传家族史。本研究经患儿家属知情同意,并报批医院伦理委员会批准。

经检查,患儿生长激素激发实验:峰值9.78 ng/mL;胰岛素样生长因子-Ⅰ:215 ng/mL;胰岛素样生长因子结合蛋白3:5 150 ng/mL;垂体泌乳素:100.82 U/mL;皮质醇(8a)162.01 nmol/L;促肾上腺皮质激素:7.9 pmol/L;肝功能:谷草转移酶46 U/L,谷丙转移酶63 U/L,碱性磷酸酶319 U/L,余项目无异常;胰岛素22.8 mU/L;餐后2 h血糖10.13 mmol/L;糖化血红蛋白5%;血常规、尿常规、水电解质、血脂、甲状腺功能等未见明显异常;乙肝两对半为阴性。后复查肝功能:谷草转移酶30 U/L,谷丙转移酶31 U/L;餐后2 h血糖6.3 mmol/L。影像学检查:左手正位片示:骨龄为9岁(G-P法);垂体MRI平扫示:未见病变征象。韦氏智力发育:言语智商34;操作智商46;总智商34。染色体核型分析:46,XX。

1.2 方 法

1.2.1 检测方法 取得父母知情同意后,抽取患儿静脉血行外周血染色体微阵列分析。采用Affymetrix公司配套检测试剂盒及优化的标准操作流程,使用CytoScanHD/CytoScan750K进行全基因组范围扫描。整个过程严格按照质控标准进行,包括DNA提取、酶切、连接、PCR、PCR产物纯化、片段化、标记、杂交、扫描和结果分析等步骤。

1.2.2 检测仪器 AffymetrixGeneChip® System 3000 Dx v.2基因芯片扫描系统。

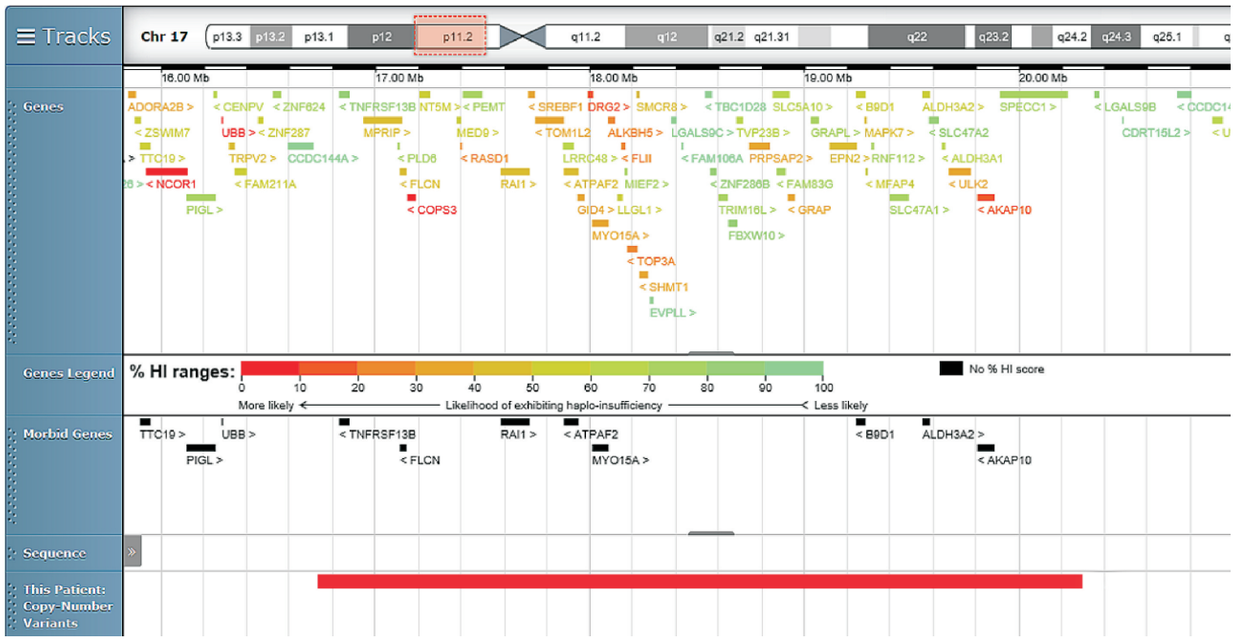
1.2.3 检测芯片 CytoScan基因芯片。

1.2.4 分析软件 Affymetrix Chromosome Analysis Suite Software;version3.0。

1.2.5 质量控制 所有实验质控标准通过的情况下,用Affymetrix Chromosome Analysis Suite Software进行分析,以Affymetrix提供的正常人DNA作为对照标准。

2 结 果

染色体微阵列分析结果示:本次检测发现患儿在chr17p11.2区域发生约3.6 Mb片段缺失(图1),包含重要功能基因RAI1,与Smith-Magenis syndrome相关。主要临床表现为轻度到中度智力低下,全面性发育迟缓,矮小身材,特殊面容,牙齿发育不良,睡眠困难,行为异常(如脾气暴躁,注意力缺陷,自残,焦虑等),患儿对疼痛和温度不敏感,可有声音嘶哑,听力、视力异常,脊柱侧凸,先



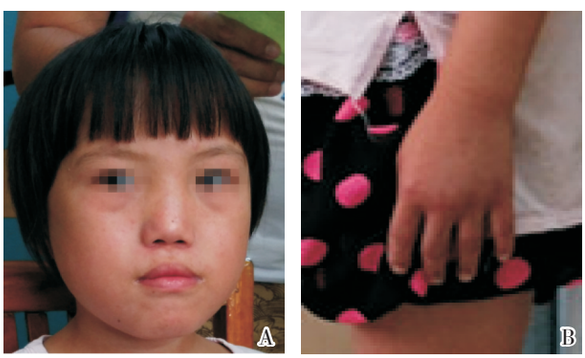
The red part represents the missing fragment.

图1　染色体微阵列分析结果

Fig.1　Result of chromosome microarray analysis

天性心脏病，肾脏发育异常等表现。

经检查，患儿身高128.3 cm（-3SD同龄同性别女童-3个标准差=136 cm），体质量24.5 kg（-0.2SD该患儿身高下同身高女童体质量的-0.2标准差），坐高/下身长：1.09，头围：53 cm（身高及体质量标准参考2005年我国九省/市儿童体格发育调查数据）。表情呆滞，特殊面容：面部稍平，上唇外翻，下颌稍前突，伸舌不配合，耳位低（图2A）。双乳BI（未青春发育状态），阴毛PH I期（未青春发育状态），手指较粗短（图2B）。结合相关文献归纳总结SMS综合征临床表现（表1）。



A：Facial Phenotype of SMS；B：Short finger of SMS

图2　SMS患儿体征

Fig.2　Signs of SMS

3　讨　论

Smith-Magenis综合征是一种罕见的遗传病，该病年龄跨度1个月至72岁[12-13]，其中大部分病例均有17p11.2片段的缺失且最常见的缺失片段大小为3.7 Mb[14]，而在decipher数据库中收录的该染色体片段的重复亦可引起一种称为Potocki-Lupski综合征的疾病，主要症状为孤独症、多动症、注意力短暂以及身材矮小等，提示该片段与生长发育及行为发育有着密切的联系。

可见，Smith-Magenis综合征的主要临床表现为特殊的面部特征，神经发育迟缓且异常，认知功能迟滞，睡眠障碍等。本文病例患儿表情呆滞，面容特殊：面部稍平，上唇外翻，下颌稍前突，伸舌不配合，耳位低，身材矮小，中度智力低下，睡眠障碍，对疼痛及温度不敏感，情绪暴躁，有自残倾向（表2），经染色体微阵列分析示：染色体17p11.2片段缺失，从而确诊为Smith-Magenis综合征。该患儿父母及胞兄拒绝行染色体及基因分析，但家庭成员体健，未表现出类似症状，该患儿缺失片段较大，考虑患儿本身基因突变可能性更大，再发风险较低，但父母再次妊娠仍需要进行产前诊断。

表1 SMS综合征主要临床表现

Table 1 Summary of the main clinical features in SMS

	Periods	Features
Facial Phenotype[15] (n=9)	/	Brachycephaly 5/9, Mid face hypoplasia 9/9, Short philtrum 9/9, Deep set eyes 6/9, Broad forehead 3/9, Small ears 6/9, Hoarse deep voice 4/9
	Infancy (n=19)	Decreased fetal movement 9/19, Hypotonia 19/19, Hyporeflexia 17/19, Increased daytime sleepiness 19/19, Delayed gross and fine motor skills 19/19, Speech delay 19/19, Sleep disorder 19/19, Dysmorphic facial appearance 19/19
Neurologic and Developmental Features[16]	Childhood	Sleep disturbance is more manifest, Language disability>90%, Hearing loss, Decreased pain sensitivity, Persisting nighttime enuresis, Developmental disorder, Mental retardation, Emotional disorder, Stereotypic behaviors, Self-injurious 96%, Bodily insertions beyond mouthing objects, Nail yanking, etc.
	Adolescents and Adults	Temper tantrums 94%, Disobedience 97%, Attention-seeking 100%, Property destruction 86%, Impulsivity 86%, Aggression 57%, hyperactivity 94%, Distractibility 89%, Toileting difficulties 80%, Sleep disturbance 94%, Self-injurious behaviors 92%, Stereotypic behaviors 100%
Cognitive Function[17]	Children	Mild or moderate mental disability, the marks of all kinds of cognitive functions is lower than the control groups' (Verbal comprehension index>Processing speed index>Perceptual reasoning index>Working memory index)
	Adults	Mild or moderate mental disability, the marks of all kinds of cognitive functions is lower than the control groups' (Processing speed index>Verbal comprehension index>Perceptual reasoning index>Working memory index)
Sleeping Trouble[18-19]	/	Decreased sleep time, Hard to fall asleep, Scattered and shortened sleep cycle, Wake up early, Early sleep onset and sleep ofset, Daytime somnolence, etc

治疗方面,该患儿因身材矮小就诊,生长激素激发试验提示生长激素部分缺乏,骨龄延迟3年,诊断生长激素缺乏症;通过病史询问排除肿瘤家族史,经详细检查排除患儿潜在肿瘤可能,予以生长激素皮下注射治疗3个月,身高改善达131.4 cm(较前增长3.1 cm)。患儿基因报告回报以后,查阅相关文献发现,Smith-Magenis综合征合并生长激素缺乏症(growth hormone deficiency,GHD)患儿,生长激素治疗不仅能有效改善矮小问题,还有改善睡眠障碍的效果[20-21]。但是患儿17p11.2缺失片段包含抑癌基因FLCN,缺失以后有潜在肿瘤风险,与患儿家长反复沟通后,目前已停用体外生长激素治疗。

遗传性疾病具有先天性的特点,既有与其他疾病相交叉的症状和体征,又有其特殊表现。当临床上表现为同时累及多个组织器官的症候群,广泛的发育落后如生长发育迟滞、精神运动发育落后、神经系统感觉异常,提示有可能为涉及较多基因的缺失或重复的染色体病、基因组病,行染色体核型分析+染色体微阵列分析有较好的诊断意义。如果临床表现强烈指向致病基因明确的单基因病或者群体致病基因谱已建立的疾病,也可以考虑直接基因检测。该病的诊治过程提示,儿童的生长发育及精神发育迟滞,早期进行基因检查有利于早期诊断,能有效地减低时间及经济成本,为家长提供可靠的遗传咨询,强调产前筛查的重要性。但至今许多基因病仍无法治愈,仅能对症治疗,期待医学的进一步发展。

(下转封三 to inside back cover)

（上接第480页　from page 480）

参考文献

[1] 周满相. Smisth-Magenis综合征一例报道并文献复习[J]. 中国优生与遗传杂志, 2016, 24(3): 95-96.
Zhou MX. A case report of one child with Smith-Magenis syndrome and literature review [J]. Chin J Birth Health Hered, 2016, 24(3): 95-96.

[2] Hou JW. Smith-Magenis syndrome: Report of one case [J]. Acta Paediatr Taiwan, 2003, 44(3): 161-164.

[3] Yeetong P, Vilboux T, Ciccone C, et al. Delayed diagnosis in a house of correction: Smith-Magenis syndrome due to a de novo nonsense RAI1 variant [J]. Am J Med Genet A, 2016, 170(9): 2383-2388.

[4] Lei TY, Li R, Fu F, et al. Prenatal diagnosis of Smith-Magenis syndrome in two fetuses with increased nuchal translucency, mild lateral ventriculomegaly, and congenital heart defects [J]. Taiwan J ObstetGynecol, 2016, 55(6): 886-890.

[5] Acquaviva F, Sana ME, Della MM, et al. First evidence of Smith-Magenis syndrome in mother and daughter due to a novel RAI mutation [J]. Am J Med Genet A, 2017, 173(1): 231-238.

[6] Slager RE, Newton TL, Vlangos CN, et al. Mutations in RAI1 associated with Smith-Magenis syndrome [J]. Nat Genet, 2003, 33(4): 466-468.

[7] Perkins T, Rosenberg JM, Le Coz C, et al. Smith-Magenis syndrome patients often display antibody deficiency but not other immune pathologies [J]. J Allergy Clin Immunol Pract, 2017, 5(5): 1344-1350.

[8] Huang WH, Guenthner CJ, Xu J, et al. Molecular and neural functions of rai1, the causal gene for Smith-Magenis syndrome [J]. Neuron, 2016, 92(2): 392-406.

[9] Diessler S, Kostic C, Arsenijevic Y, et al. Rai1 frees mice from the repression of active wake behaviors by light [J]. Elife, 2017, 6: e23292.

[10] Poisson A, Nicolas A, Sanlaville D, et al. Smith-Magenis syndrome is an association of behavioral and sleep/wake circadian rhythm disorders [J]. Arch Pediatr, 2015, 22(6): 638-645.

[11] 王莹洁, 张淑梅. 在Smith-Magenis综合征中具有诊断意义的手异常: 4例del(17)(p11.2 p11.2)新患者[J]. 国外医学·遗传学分册, 1992(3): 167-168.
Wang YJ, Zhang SM. The feature of the hand abnormality in Smith-Magenis syndrome has diagnostic significant: 4 new patients with the deletion in the chr17p11.2 region [J]. Foreign Med Sci (Sect Genet), 1992(3): 167-168.

[12] Chen L, Mullegama SV, Alaimo JT, et al. Smith-Magenis syndrome and its circadian influence on development, behavior, and obesity-own experience [J]. Dev Period Med, 2015, 19(2): 149-156.

[13] 沈理笑, 张劲松, 季星, 等. Smith-Magenis综合征一例临床及遗传学研究[J]. 中华儿科杂志, 2012, 50(3): 227-230.
Shen LX, Zhang JS, Ji X, et al. Clinical and genetic study of a case with Smith-Magenis syndrome [J]. Chin J Pediatr, 2012, 50(3): 227-230.

[14] Vilboux T, Ciccone C, Blancato JK, et al. Molecular analysis of the retinoic acid induced 1 gene (RAI1) in patients with suspected Smith-Magenis syndrome without the 17p11.2 deletion [J]. PLoS One, 2011, 6(8): e22861.

[15] Gupta R, Gupta N, Nampoothiri S, et al. Smith-Magenis syndrome: Face speaks [J]. Indian J Pediatr, 2016, 83(6): 589-593.

[16] Gropman AL, Duncan WC, Smith AC. Neurologic and developmental features of the Smith-Magenis syndrome (del 17p11.2) [J]. Pediatr Neurol, 2006, 34(5): 337-350.

[17] Osorio A, Cruz R, Sampaio A, et al. Cognitive functioning in children and adults with Smith-Magenis syndrome [J]. Eur J Med Genet, 2012, 55(6-7): 394-399.

[18] Spruyt K, Braam W, Smits M, et al. Sleep complaints and the 24-h melatonin level in individuals with Smith-Magenis syndrome: Assessment for effective intervention [J]. CNS Neurosci Ther, 2016, 22(11): 928-935.

[19] Chen L, Mullegama SV, Alaimo JT, et al. Smith-Magenis syndrome and its circadian influence on development, behavior, and obesity - own experience [J]. Dev Period Med, 2015, 19(2): 149-156.

[20] Itoh M, Hayashi M, Hasegawa T, et al. Systemic growth hormone corrects sleep disturbance in Smith-Magenis syndrome [J]. Brain Dev, 2004, 26(7): 484-486.

[21] Spadoni E, Colapietro P, Bozzola M, et al. Smith-Magenis syndrome and growth hormone deficiency [J]. Eur J Pediatr, 2004, 163(7): 353-358.

（编辑　余　菁）