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·病例报告·

以视网膜错构瘤为首发特征的早产儿结节性硬化症1例

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[摘　要]　结节性硬化症(tuberous sclerosis complex，TSC)是一种累及多系统的常染色体显性遗传病，早期呈单一表现，容易漏诊、误诊，以眼部症状为首发特征的新生儿期病例少有报道。本文报告1例早产男婴，出生后1 d眼底筛查发现右眼视网膜散在多个灰白色半透明隆起灶及脱色素斑，回溯胎儿期超声心动图异常高度怀疑TSC，进一步行头颅MRI检查及家族基因检测，在新生儿期明确了这一诊断。

[关键词]　视网膜错构瘤；结节性硬化症；早产儿

Tuberous sclerosis complex presenting as retinal hamartomas in a preterm infant: A case report

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Abstract　Tuberous sclerosis complex is a multisystemic disease with an autosomal dominant inheritance pattern. Missed diagnosis and misdiagnosis are common for patients with single manifestation in the early stage. There are few documented neonatal cases with ocular symptoms as primary presentation. Here we report a newborn boy presented with retinal hamartoma, retinal achromic patch, fetal cardiac rhabdomyoma and subependymal nodules. Subsequent genetic tests confirm a diagnosis of TSC.

Keywords　retinal hamartoma; tuberous sclerosis complex; preterm infant

结节性硬化症(tuberous sclerosis complex，TSC)是常染色体显性遗传病，累及脑、皮肤、心、眼、肾等多个器官，发病率为1/6 000~1/10 000[1]。该病特征隐匿，多无临床症状，新生儿期诊断困难，漏诊率高达25%~39%[2-3]。目前，TSC平均确诊年龄为7.5岁[3]，以癫痫发作、智能减退和面部皮脂腺瘤为主要特征。1岁以内确诊的TSC患儿首发特征主要为心脏横纹肌瘤、癫痫、脱色素斑和家族史[4]。本文报道1例早产男婴，生后1 d眼底检查发现视网膜错构瘤，回溯胎儿期超声

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心动图早期诊断TSC。

1 临床资料

患儿男，因“胎儿宫内窘迫”于孕34^{+4}周剖宫产娩出，Apgar's评分9-10-10。因早产于生后1 d用Retcam III常规行眼底检查，发现右眼视盘颞侧、下方及鼻侧距视盘2个视盘直径(papillary diameter，PD)处分别可见一类圆形、半透明的隆起病灶，呈灰白色，边界清晰，大小分别为3×2.5 PD、1.5×1.5 PD、1×1 PD，颞下和鼻上方网膜见脱色素斑(图1)。右眼B超发现两处视网膜强回声隆起带，呈半球形，凸向玻璃体腔，范围分别为4.0 mm×1.1 mm和2.8 mm×0.8 mm(图2)。回顾患儿母亲的产检资料，孕32周胎儿超声心动图提示其左室侧壁、室间隔、右室侧壁多个高回声团(图3A)。立即行脐血穿刺21、18、13及X/Y染色体QF-PCR检查、脐血染色体与微阵列分析，未见明显异常。生后2 d复查超声心动图，提示左室侧壁、室间隔、右室侧壁多个高回声团，左室侧壁最大约5.0 mm×7.8 mm，室间隔最大约8 mm×5 mm，右室侧壁7 mm×7 mm(图3B)。为排除颅内异常行头颅MRI检查，提示双侧脑室室管膜下结节状异常信号，T1WI FLAIR呈高信号，T2WI FLAIR呈低信号(图4)。双肾、输尿管及肝胆脾胰B超未见明显异常。脑电图、心电图未见明显异常。血常规、肝肾功能、电解质等实验室检查未见明显异常。皮肤无脱色斑改变。根据患儿Retcam III、超声心动图及头颅MRI 检查结果，诊断为结节性硬化。经家属同意采集患儿及父母血标本行TSC相关基因检测。利用高通量二代测序方法，发现患儿TSC2基因(NM-000548)第20号外显子c.2194C>T(p.Q732*)杂合突变(图5A)。父亲检测到相同的突变位点(图5B)，体格检查发现智力减退和颜面部色素脱失斑。

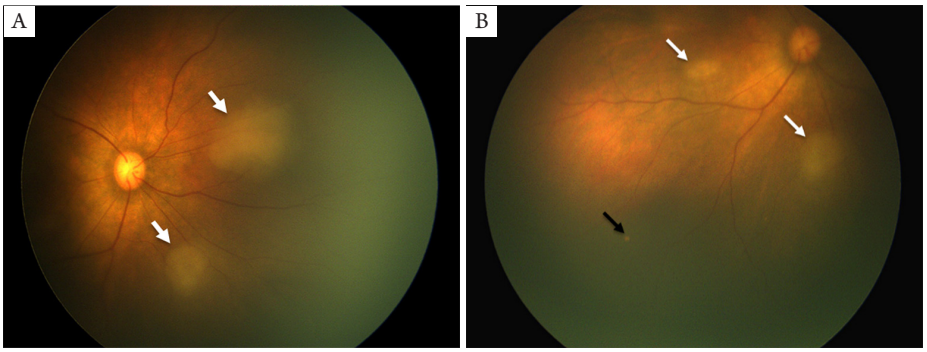

图1 TSC患儿右眼Retcam-III检查(白色箭头：多发视网膜错构瘤；黑色箭头：视网膜脱色素斑)

Figure 1 Retcam-III examination of the right eye in the child with TSC (white arrows: multiple retinal hamartomas; black arrow: retinal depigmentation spot)

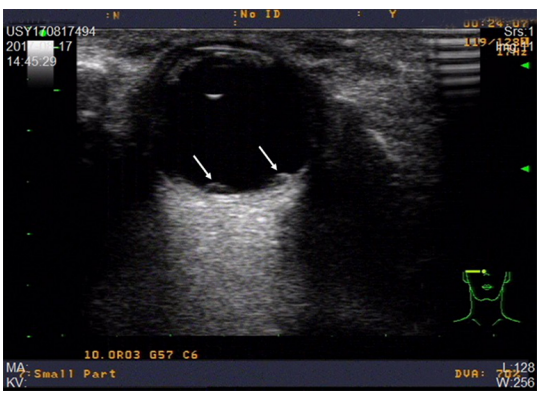

图2 TSC患儿右眼B超检查示隆起的强回声带，凸向玻璃体腔(白色箭头)

Figure 2 B-ultrasound examination of the right eye of the child with TSC shows a strong echo zone protruding towards the vitreous cavity (white arrows)

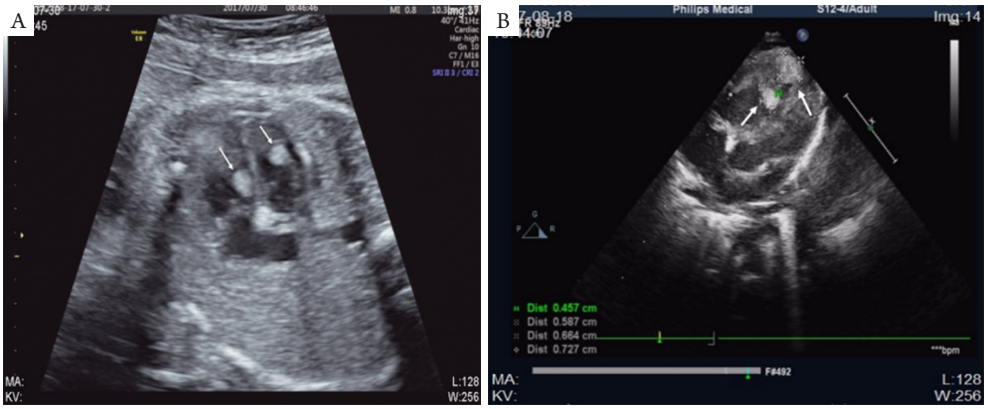

图3 胎儿期(A)及出生后(B)心脏超声检查示多发横纹肌瘤(箭头)

Figure 3 Fetal (A) and postnatal (B) cardiac ultrasound show cardiac rhabdomyomas (arrows)

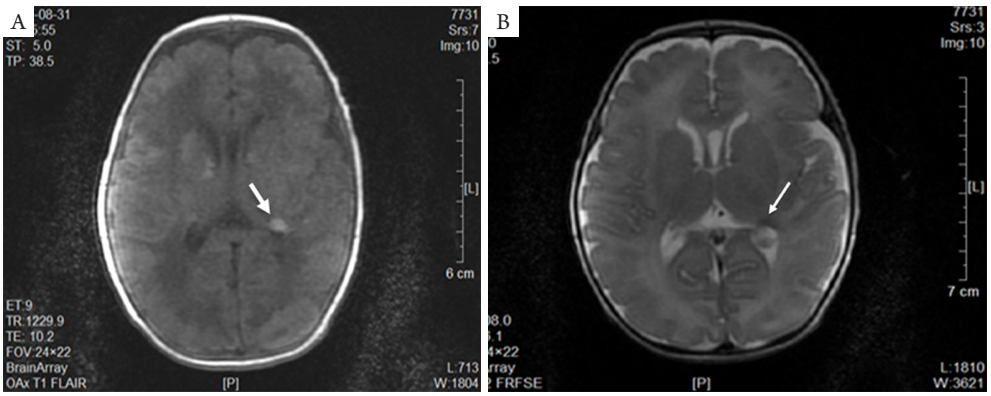

图4 TSC患儿头颅MRI提示双侧脑室室管膜下结节状异常信号(箭头)

Figure 4 Head MRI of child with TSC shows abnormal nodular signals in bilateral ventricles (arrows)

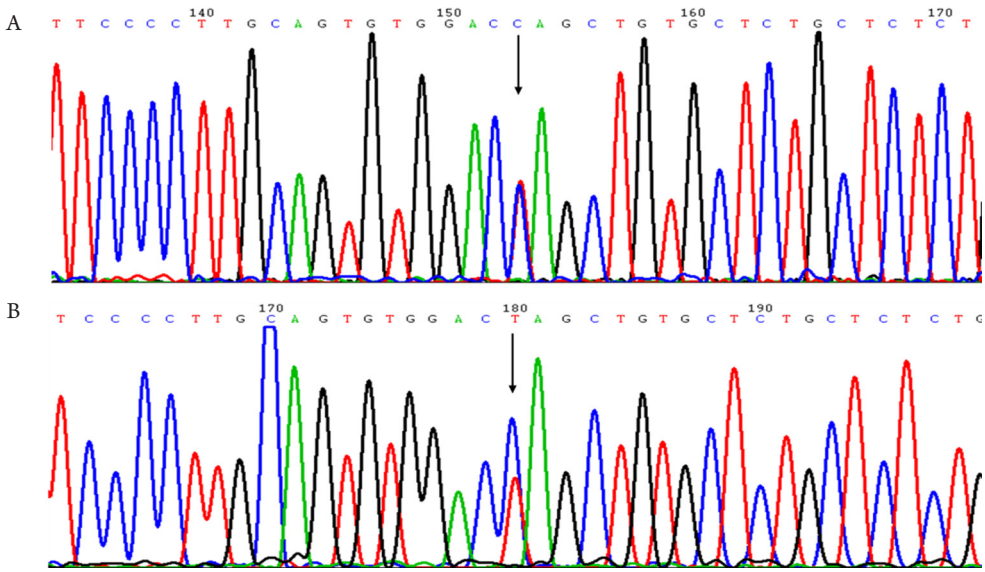

图5 患儿(A)及其父亲(B)的基因测序图

Figure 5 Gene sequencing map of the child (A) and his father (B)

2 讨论

TSC是多系统疾病，大多隐匿发生并不断加重，预后差，在临床表现出现前予以合理干预和治疗，可明显提高治疗效果，改善生活质量。目前，TSC的平均确诊年龄为7.5岁，10岁前确诊的患者占81%[3]，以癫痫发作、智能减退和面部皮脂腺瘤为主要特征，其中80%~90%以癫痫为首发症状[5]。胎儿影像学技术及产前基因检测技术的提高使TSC的确诊提前到胎儿期或新生儿期，相关研究[4]表明：1岁以内确诊的TSC患儿首诊原因为心脏横纹肌瘤(56%)、癫痫(34%)、脱色素斑(15%)和家族史(12%)。受技术普及程度及医生认识所限，胎儿期或新生儿期确诊TSC较困难。本例患儿为早产儿，首发特征为视网膜错构瘤，在胎儿期及出生后的检查中发现3个主要特征(视网膜错构瘤、心脏横纹肌瘤和室管膜下结节)和1个次要特征(视网膜脱色素斑)，考虑诊断为TSC[1]，随后的基因检测证实了这一诊断。

TSC患者眼部特征为视网膜错构瘤和视网膜脱色素斑，以男性多见，容易漏诊[6]，合并视网膜病变的患者认知障碍和癫痫的发病率明显高于其他患者，预后较差[7]，目前无法通过产前诊断技术发现胎儿的眼部病变，因此TSC高危胎儿(有家族史或发现胎儿期心脏肿物、肾脏肿物、脑部异常等)出生后立即检查眼底，为预防性治疗提供临床依据。

心脏横纹肌瘤最早可于胎儿期15周发现，大多数在胎儿期20~30周被胎儿超声心动图检出[8]。Staley等[3]对22例出生后1周内确诊TSC的患儿进行回顾性研究，发现16例(73%)于胎儿期发现心脏横纹肌瘤，3例因出生后心功能异常而发现心脏横纹肌瘤。Chen等[9]对53例胎儿心脏肿物的患儿进行基因研究发现：86%的多发性心脏肿物胎儿和31%的单发心脏肿物胎儿携带TSC1或TSC2突变。

胎儿头部MRI和超声检查均可发现TSC病变，前者敏感性高[10]，但技术要求高，尚未得到普及应用。室管膜下结节的MRI特征为T1WI呈高信号，T2WI呈低信号，本病例与之相符。随着年龄增长及脑白质髓鞘化，多数结节消退或者钙化，少数逐渐增大转变为室管膜下巨细胞星形细胞瘤，引起梗阻性脑积水，需手术治疗，故本研究中的患儿应每2~3年复查头颅MRI[11]。

肿瘤抑制基因TSC1和TSC2是TSC的致病基因。2012年国际TSC联盟修订的最新诊断标准将基因诊断作为独立的诊断标准。本例患儿为TSC2基因c.2194C>T的无义突变，该突变导致蛋白翻译提前终止产生截短蛋白。此突变之前已被报道[12]。此家系的基因突变类型较为少见，追溯其父亲的临床症状，表现为发现智力减退和颜面部色素脱失斑。既往研究[7,13-14]认为：临床表型与基因变异的类型和位置有关，伴眼部体征的患者TSC2基因变异较常见[7]；有家族史患者以TSC1无义突变或移码突变为主，症状较散发病例轻[13]；TSC2变异较TSC1变异的患儿在婴儿期更容易出现运动、语言、认知等发育迟缓[14]。

胎儿超声心动图、头颅MRI及基因检测可以诊断胎儿期TSC，降低TSC患儿的出生率，促进优生优育。对出生后的TSC高危患儿进行视网膜检查是早期诊断及评估预后的一个重要手段，应得到临床医生的重视。

开放获取声明

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