

EEF1A2基因变异致发育性癫痫性脑病33型1例

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[摘要] 患儿, 男, 7月龄, 表现为重度全面发育落后、难治性癫痫、肌张力降低、眼球震颤、眼距宽、鼻梁塌陷、上唇外翻、高腭弓和隐睾, 基因检测发现 *EEF1A2* 基因存在 c.364G>A(p.E122K) 新生杂合错义变异, 最终该患儿确诊为 *EEF1A2* 基因变异致常染色体显性遗传发育性癫痫性脑病33型。该病例报道提示, 对不明原因婴儿期起病的重度-极重度全面发育落后/智力障碍、难治性癫痫患儿, 尤其是存在肌张力低下、语言缺失、颅面部畸形者, 应考虑 *EEF1A2* 基因变异可能, 应尽早完善遗传学检测协助诊断。

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[关键词] 全面发育落后; 智力障碍; 癫痫; *EEF1A2* 基因; 婴儿

Developmental and epileptic encephalopathy 33 caused by *EEF1A2* gene mutation: a case report

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Abstract: A boy, aged 7 months, presented with severe global developmental delay (GDD), refractory epilepsy, hypotonia, nystagmus, ocular hypertelorism, a broad nasal bridge, everted upper lip, a high palatal arch, and cryptorchidism. Genetic testing revealed a *de novo* heterozygous missense mutation of c.364G>A(p.E122K) in the *EEF1A2* gene, and finally the boy was diagnosed with autosomal dominant developmental and epileptic encephalopathy 33 caused by the *EEF1A2* gene mutation. This case report suggests that for children with unexplained infancy-onset severe to profound GDD/intellectual disability and refractory epilepsy, genetic testing for *EEF1A2* gene mutations should be considered. This is particularly important for those exhibiting hypotonia, nonverbal communication, and craniofacial deformities, to facilitate a confirmed diagnosis. [Chinese Journal of Contemporary Pediatrics, 2024, 26(8): 861-864]

Key words: Global developmental delay; Intellectual disability; Epilepsy; *EEF1A2* gene; Infant

患儿, 男, 7月龄, 因发育落后、抽搐4个月就诊。患儿3月龄不能抬头, 并出现抽搐, 表现为大叫一声后, 意识丧失, 双眼上翻, 双手握拳, 面色口唇发绀, 持续数十秒, 发作时测体温37.5℃, 当日共发作3次, 未予特殊处理。4月龄再次出现抽搐, 发作形式及持续时间与之前相同, 遂至当地医院住院, 完善4 h脑电图示多量广泛尖波、棘波、多棘波阵发。头颅磁共振成像示内囊前肢髓鞘化落后于月龄, 胼胝体细薄 (图1)。诊断为“癫痫、发育落后”, 予左乙拉西坦 (每日

40 mg/kg) 治疗, 仍有反复发作, 1~2次/周。4个月20 d加用托吡酯 (每日3 mg/kg), 发作改善不明显。6月龄出现发呆愣神, 双眼凝视, 呼之不应。7月龄出现间断双侧眼球水平震颤, 抬头仍不稳, 不会独坐、翻身、爬, 不能“咿呀”发音。为进一步诊治, 来我院就诊。既往有反复呼吸道感染病史。患儿系第2胎第2产, 胎龄39周, 因“疤痕子宫”剖宫产娩出, 无抢救窒息史, 出生体重3.1 kg, 生后混合喂养。母亲孕期身体健康, 否认毒物、放射线接触史。父母身体健康, 否认近亲

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婚配，有一同母异父哥哥，身体健康，否认家族有神经精神疾病或遗传病史。

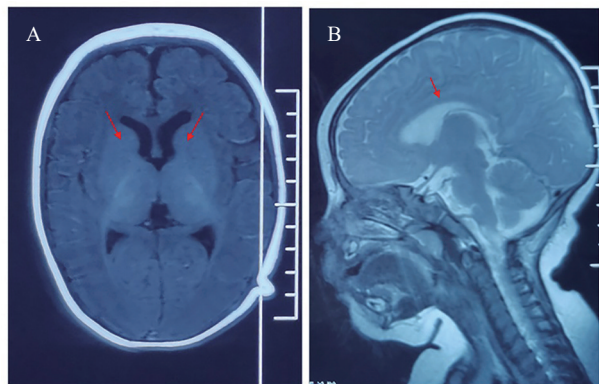


图1 先证者4月龄时头颅磁共振成像检查结果 图A为T₁加权像，内囊前肢髓鞘化落后于月龄；图B为T₂加权像，胼胝体细薄。箭头所示为病变位置。

体格检查：体重10 kg ($P_{75} \sim P_{90}$)，身长79 cm ($>P_{97}$)，头围45 cm (P_{75})。前囟平软，约0.5 cm × 0.5 cm。神志清楚，反应迟钝，追光、追物、追声欠佳，偶可逗笑，双眼球间断有水平震颤，不能抓物，眼距宽，鼻梁塌陷、上唇外翻、高腭弓。心肺腹检查未见异常。四肢肌力正常，四肢肌张力稍降低，腱反射未引出，病理征阴性，手掌、脚掌脱皮。双侧阴囊未触及睾丸。

辅助检查：入院后血常规、尿常规、肝功能、肾功能、心肌酶、电解质、血脂、动脉血气分析、血乳酸、血糖、血氨基酸和酰基肉碱筛查未见异常。7月龄4 h视频脑电图示弥漫性大量2~5 Hz混合活动低-中波幅，发作间期睡眠期广泛性棘慢波/尖慢波。家系全外显子组测序示 $EEF1A2$ 基因4号外显子存在c.364G>A(p.E122K) (NM_001958.5) 杂合错义变异。Sanger测序示患儿父母该位点均为野生型，提示该变异为新生变异(图2)。本例患儿是第364位核苷酸G突变为A，导致其编码的蛋白第122位谷氨酸变成赖氨酸，依据美国医学遗传学与基因组学学会变异分类标准与指南^[1]，该变异评定为致病性变异(PS1+PS2+PS3+PM1+PM2)。

结合临床特点及辅助检查，最终该患儿诊断为：(1) 常染色体显性遗传发育性癫痫性脑病33型(developmental and epileptic encephalopathy 33, DEE33)；(2) 隐睾。将患儿托吡酯加量至5 mg/(kg·d)，发作减少，7~10 d发作1次。1岁1月龄发作频率增加，4 h视频脑电图示清醒期、睡眠

期双侧后头部为主多灶性或广泛性尖波、棘波、棘慢波/尖慢波、多棘慢波，清醒期全面性发作、肌阵挛发作，加用丙戊酸钠(每日20 mg/kg)，仍有反复发作，表现为全身抖动一下，持续2~3 s，每小时发作数次。1岁3月龄加用氯巴占(每日10 mg)，左乙拉西坦减量，发作减少，每日发作数次，表现为白天入睡前出现轻微点头。随访至1岁8个月，患儿对外界反应好转，追光、追物可，能“咿呀”发音，会无意识发“baba、mama”音，不能听懂简单指令，抬头稳，不能翻身、独坐、独走，持物差，四肢肌张力偏低，腱反射未引出，病理征阴性。双侧阴囊未触及睾丸。

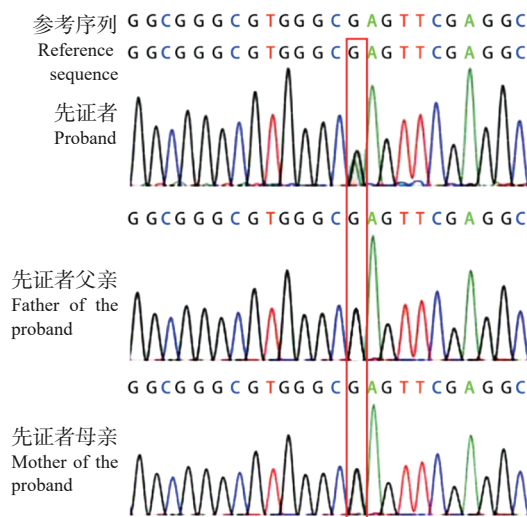


图2 患儿及其父母 $EEF1A2$ 基因Sanger测序图 先证者 $EEF1A2$ 基因存在c.364G>A(p.E122K)杂合变异，父母均为野生型。红框内为突变位点。

讨论： $EEF1A2$ 基因定位于人类染色体20q13.3，编码真核细胞翻译延长因子1 α 2(eukaryotic translation elongation factor 1, α -2, eEF1A2)。 $EEF1A2$ 是常染色体显性遗传DEE33和常染色体显性遗传智力障碍38型的致病基因。真核细胞翻译延长因子1 α 有两种同分异构体，即eEF1A1和eEF1A2，分别由 $EEF1A1$ 和 $EEF1A2$ 基因编码，其通过促进氨基酰tRNA与核糖体A位点的结合，对蛋白质合成过程新生多肽的延伸发挥重要作用^[2]。eEF1A1在各种组织中广泛表达；eEF1A2在脑、心肌、骨骼肌中特异表达^[3]。eEF1A1在整个发育过程中均广泛表达，但出生后在神经元、骨骼和心脏中表达量下降，最终被eEF1A2完全取代^[3]，这个过程在小鼠出生后21 d左右完成。

eEF1A1和eEF1A2的互斥表达与*Eef1a2*基因敲除小鼠断奶前表现正常,约生后21 d开始出现震颤、共济失调、伴或不伴自发性癫痫发作,28 d内死亡相符^[4]。

2012年de Ligt等^[5]首次报道1例*EEF1A2*基因错义变异导致重度智力障碍(intellectual disability, ID)和癫痫患者。迄今为止,英文文献共报道41例*EEF1A2*基因变异患者^[6-18],未见相关中文病例报道。包括本文病例,共42例*EEF1A2*基因变异患者,男性17例,女性23例,2例未描述性别,报道时年龄为1岁3个月至32岁^[6-18]。*EEF1A2*基因共有18种不同变异位点,均为错义变异,无移码、剪接、无义等功能缺失变异^[6-18]。这种独特的基因变异谱提示,*EEF1A2*基因杂合功能丧失性变异可能导致人类胚胎致死,或者人类可以耐受*EEF1A2*基因杂合功能丧失性变异,也提示*EEF1A2*基因杂合错义变异可能是通过功能获得或显性负效应致病。18种*EEF1A2*基因变异散布在整个基因的编码序列中,无明确的基因型-表型相关性^[6-18]。42例*EEF1A2*基因变异患者均有全面发育落后(global developmental delay, GDD)/ID,以重度-极重度为主,多数患者存在语言缺失、难治性癫痫、肌张力降低、运动障碍、面部外观异常、小头畸形等^[6-18]。该病预后差,多数癫痫发作难以控制,已报道4例死亡病例,2例死于神经退行性病变^[7],2例死于心力衰竭^[6],因此*EEF1A2*基因变异患者除了神经功能评估,还应进行心脏功能评估。本例患儿以重度GDD、语言缺失、早发难治性癫痫、四肢肌张力低下、眼球震颤、面部外观异常和隐睾为主要表现,*EEF1A2*基因存在c.364G>A(p.E122K)新生杂合错义变异,该变异已在8例患者中报道^[7-9, 12, 16]。文献报道的8例p.E122K变异患者均存在中度-重度GDD/ID和癫痫发作,7例语言缺失,5例肌张力低下,6例颅面部外观异常^[7-9, 12, 16]。本例患儿临床表现与文献报道的8例p.E122K变异患者临床表型相符,因此,结合临床表现及基因检测结果最终确诊为常染色体显性遗传DEE33。

综上所述,*EEF1A2*基因变异患者临床特点为婴儿期起病,重度-极重度GDD/ID、语言缺失、难治性癫痫、肌张力减低、颅面畸形等。该病预后差,可因心力衰竭和神经退行性病变导致早期死亡,因此*EEF1A2*基因变异患者都应进行神经功能和心脏功能评估。

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