·论著·

46,XY DSD伴发抗NMDAR脑炎1例及文献复习*

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【摘要】**目的** 探讨性发育异常(DSD)与抗NMDAR脑炎可能的潜在关联及机制。**方法** 回顾1例46,XY DSD伴发抗NMDAR脑炎患者的临床资料及诊查经过，结合国内外文献分析二者关联可能性，并推测潜在机制。**结果** 患者26岁女性(社会性别)，因癫痫持续状态入住神经内科，脑电图：全导联极度δ刷，脑脊液及血清抗NMDAR抗体滴度均为1:16，明确抗NMDAR脑炎。查体还发现乳房未发育、女外生殖器外观幼稚，盆腔磁共振增强扫描及彩超检查未发现性腺及内生殖器官，测染色体核型：46,XY，明确46,XY DSD，遗传学性别男性。结合相关文献，可疑抗NMDAR脑炎与DSD的性腺生殖细胞分化异常相关，详细彩超探查发现腹股沟区隐睾，考虑癌变风险建议切除，但患方拒绝。**结论** DSD为染色体核型对应的性腺或生殖器表型不一致的罕见遗传病，性腺肿瘤风险逐年增高。抗NMDAR脑炎属少见自身免疫病，可见于卵巢畸胎瘤的女性及睾丸癌的男性。DSD患者伴发抗NMDAR脑炎可能病机为性腺生殖细胞分化异常后诱导神经系统自身免疫的激活。

【关键词】性发育异常；抗NMDAR脑炎；自身免疫
【中图分类号】R512.3
【文献标识码】A
【基金项目】福建省自然科学基金(2020J011305)；福建医科大学启航基金(2021QH1253)；福建医科大学教育教学研究项目(J22023)
DOI:10.3969/j.issn.1009-3257.2022.12.002

46,XY Disorders of Sex Development Accompanied by Anti-NMDAR Encephalitis: A Case Report and Literature Review*

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Abstract: ***Objective*** To explore the possible connection and mechanism between Disorders of Sex Development (DSD) and anti-NMDAR encephalitis.***Methods*** The clinical data and diagnosis process of a patient with 46,XY DSD accompanied by anti-NMDAR encephalitis were reviewed. The possible connection between these two rare diseases was analyzed based on the domestic and foreign literature, and the potential mechanism was speculated. ***Results*** The patient was a 26-year-old female (social gender) who was admitted to the neurology department due to status epilepticus. Dynamic EEG showed a large number of synchronous extreme delta brushes in bilateral whole leads, and anti-NMDAR antibody titers in cerebrospinal fluid was 1:16 as same as in serum, so that anti-NMDAR encephalitis was diagnosed clearly. Undeveloped breast, immature female external genital appearance, absence of pubic hair was found by physical examination. No gonads and internal reproductive organs were found by the contrast-enhanced pelvic magnetic resonance scan and color Doppler ultrasound. The patient was further tested for karyotype that showed chromosome is 46, XY, so 46, XY DSD was diagnosed, and the genetic gender was male. According to relevant literature evidence, we suspected that the occurrence of anti-NMDAR encephalitis is associated with abnormal gonadal germ cell differentiation in DSD. With further test for inguinal and labia ultrasonography, it was found that there were atrophic cryptorchidisms in the bilateral inguinal. Considering the risk of cancer, we recommended to remove cryptorchidisms, but it was refused by patient's family. ***Conclusion*** DSD is a rare congenital genetic disease with inconsistent gonad or genital phenotype corresponding to the chromosome karyotype, and the risk of gonadal tumor increases with age. Anti-NMDAR encephalitis is a rare autoimmune disease that is common in women with ovarian teratoma and testicular cancer in men. The pathogenesis of Anti-NMDAR encephalitis in DSD patients may be that the activation of nervous system autoimmunity was induced by abnormal gonadal germ cell differentiation.

Keywords: Abnormal Sexual Development; Anti-NMDAR Encephalitis; Autoimmunity

1 病例资料

患者社会性别女性，26岁，汉族，未婚，因突发腹痛伴呕吐3小时急诊我院。就诊时神志清楚，体温正常，无神经系统及精神症状，腹部查体未见明显异常。在检查过程中逐渐出现躁动不安、胡言乱语，约半小时后，突然强直阵挛性发作，立即予地西泮对症后停止。平素体健。15岁时曾因一直无月经来潮就诊医院，检查发现无子宫发育，但无进一步诊治。辅助检查：血常规、生化、CPR、血淀粉酶、脂肪酶、肝胆胰脾彩超、颅脑CT和颅脑磁共振均未见明显异常。入住神经内科后仍反复强直阵挛性发作，抗癫痫效果不佳。首次腰椎穿刺，测颅内150mmH_2O，脑脊液化验示：白细胞35×106/L、红细胞未见、葡萄糖3.23mmol/L、氯125.2mmol/L、蛋白定量42.1mg/dl，并外送自身免疫性脑炎相关抗体及病毒基因二代测序。监测长程动态脑电图示：双侧全导联大量同步性极度δ刷(规律δ波基础上叠加的β波，详见Fig1)。首次经验性治疗方案：阿昔洛韦0.5g 1/8h、甲泼尼龙琥珀酸钠1g qd、丙种球蛋白20g qd)，并予丙戊酸钠、咪达唑仑、苯巴比妥积极抗癫痫。3天后外送结果回报示：脑脊液抗NMDAR抗体滴度1:16，血清NMDAR抗体滴度1:16，其余指标(AMPA1、AMPA2、LGI1、IgLON5、DRD2、DPPX、GlyR1、GAD65、CASPR2、GABAB和mGluR5)均阴性，脑脊液病毒基因二代测序阴性。随修正治疗方案：停阿昔洛韦，继续激素及丙种球蛋白冲击治疗满5天，随后激素逐渐减量。

因查体同时发现患者乳房无发育、女性外生殖器外观幼稚、无阴毛，故行盆腔磁共振增强扫描及彩超检查未发现任何性腺及内生

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殖器官，予进一步测染色体核型示：46,XY，故诊断46,XY DSD，遗传学性别为男性。性激素化验示：雌二醇140 pmol/L、促卵泡激素62.81IU/L、促黄体激素31.43IU/L、孕酮32.54nmol/L、催乳素259.36mIU/L、睾酮0.38nmol/L，提示睾酮水平降低，促卵泡激素和促黄体激素无降低，故非垂体功能不全引起性腺发育异常，可能睾丸病变所致。为明确是否残存睾丸，对腹股沟及阴唇等易隐藏睾丸的位置详细彩超探查，发现双侧腹股沟区各存在萎缩的隐睾。考虑隐睾存在演变恶性肿瘤风险，建议切除，但患者拒绝。

第25天出院，患者仅遗留轻微性格改变症状，未再出现癫痫发作1周，无其他神经精神症状。出院后继续服用小剂量激素及抗癫痫药(氯硝西泮、托吡酯和左乙拉西坦)，嘱定期随访逐步减量，随访至今无复发。

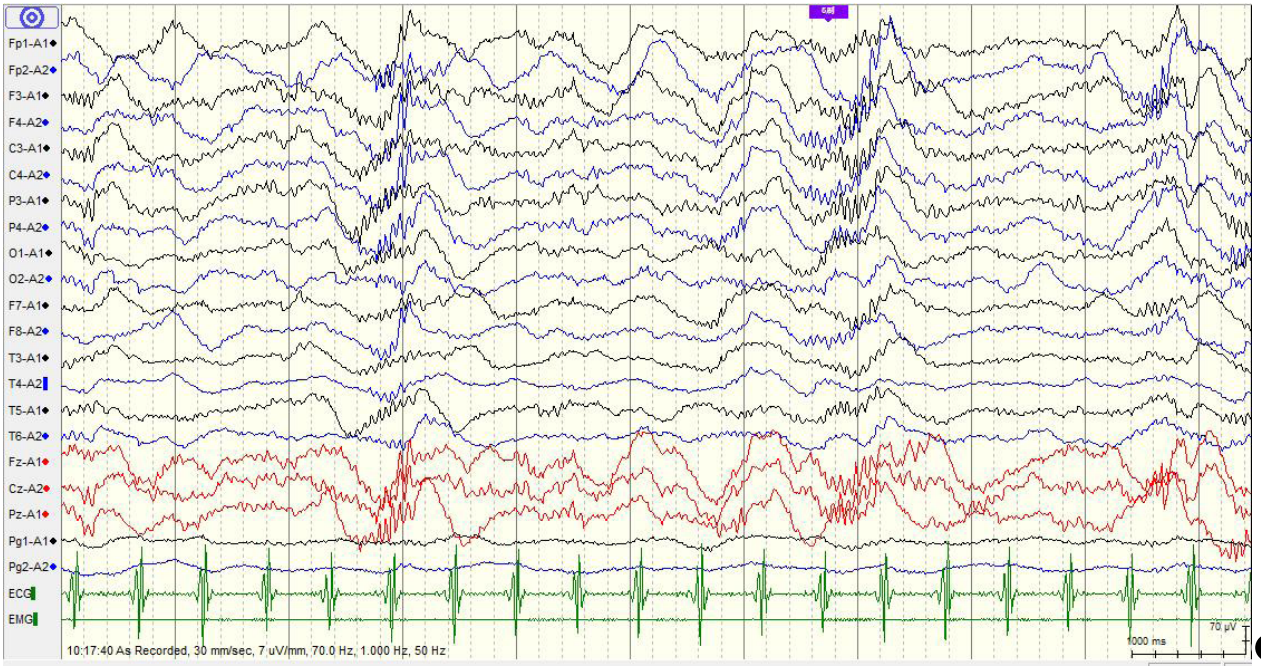

图1 脑电图显示极具节律性的δ刷型，沿δ波覆盖有节律性β频率活动的爆发。(标准10/20导联，高频滤波器=70Hz，低频滤波器=0.5Hz，陷波滤波器=关闭，灵敏度=7μV/mm，显示速度=30mm/s)。

2 讨 论

抗NMDA受体(anti-NMDA receptor，NMDAR)脑炎是一种免疫介导性疾病，其表现特征是复杂的神经精神综合征[1]。Vitaliani等[2]于2005年首次报道4位良性畸胎瘤的年轻女性患者均出现精神障碍、肺通气不足、癫痫等类似症状，考虑为免疫介导的新型的副肿瘤性边缘性脑炎，相关抗体可能与表达于海马神经细胞膜的不明抗原相互作用。随后Dalmau等[3]报道多例此类患者，且在血清及脑脊液中发现作用于海马和前额叶神经细胞膜上表达的NMDAR抗体，并于2007年首次提出副肿瘤性抗NMDAR脑炎的概念。抗NMDAR脑炎发病率不高，大约每百万人1~5人，80%的患者为女性，多数与畸胎瘤相关[1]。Titulaer等对577例抗NMDAR脑炎的研究显示，患者平均年龄为21岁，其中211例(37%)年龄<18岁，但伴发畸胎瘤者发病率随年龄的增长而升高，81%的患者为女性[4]。

NMDAR是一类主要表达于人体大脑边缘系统的配体门控型谷氨酸受体,是异四聚体离子型受体，由2个GluN1亚单位和2个GluN2或GluN3亚单位组成，主要分布于海马、前脑及边缘系统[3]，具有调控中枢神经系统突出传递、调节突触可塑性、参与学习和记忆等重要功能。抗NMDAR脑炎患者血清和脑脊液中存在针对中枢神经系统NMDAR中的NR1亚基的特异性IgG抗体[5]，能够导致受体内化(即由突触后膜表面转移到细胞内)，可逆性减少突触后膜表面受体的密度[6]，减弱受体介导的突触电流[7]，使得NMDAR的功能受损。典型抗NMDAR脑炎主要症状可分成8组，包括精神和行为异常、癫痫发作、运动功能障碍、记忆障碍、言语障碍、意识水平下降、自主神经功能障碍、中枢性低通气等[4]。其诊断需结合病史、临床表现、脑电图及脑脊液检查等，脑脊液中检出NMDAR的抗体可明确诊断[8]。本例患者出现急性进展的精神障碍、意识水平下降及反复癫痫发作，EEG发现特异性的极度δ刷，脑脊液及血清中的抗NMDAR抗体均阳性，符合抗NMDAR脑炎的诊断标准。值得一提的是，虽然抗体在确诊中很重要，但抗体滴度变化与病程无明显相关，无法决定治疗方案或预测转归[1]。例如本例监测抗体滴度较低，但症状严重且进展迅速。

90%抗NMDAR脑炎可出现脑电图异常，通常为非特异性慢波异常，但极度δ刷状波是抗NMDAR脑炎较为特异表现[9]。本例早期脑电图检查即发现极度δ刷状波，结合入院前的起始症状及病情进展，故已开始高度怀疑抗NMDAR脑炎，并早期经验性大剂量激素及丙种球蛋白冲击治疗。抗NMDAR脑炎的脑部磁共振检查并没有特异性，且阳性率低。因此，本研究认为早期脑电图的动态检查最为重要，极度δ刷的发现可为临床诊断提供重要线索，尤其是当抗体检测结果尚未回报时，即可早期启动经验性抗免疫治疗，往往可以迅速控制病情进展并取得较好预后。一些研究[10-11]认为极度δ刷通常提示住院时间的延长、癫痫发作频率的增加、磁共振检查的异常、对免疫治疗的不敏感及不良的预后。但本例患者住院时间并不长，抗癫痫效果良好(治疗过程中δ刷并无明显变化)，磁共振检查未见明显异常，免疫治疗敏感，最终预后良好。这些与文献报道不一致的现象可能和及时积极启动抗免疫治疗关系密切。事实上，相似情况报道也越来越多[12-13]，可见仅从极度δ刷判断病情及预后并不敏感，需要后期更多更科学的队列研究。

抗NMDAR脑炎主要诱因之一是肿瘤，最常见为畸胎瘤。Titulaer等[4]对577例抗NMDAR脑炎患者分析发现38%合并有肿瘤，其中卵巢畸胎瘤最为常见，占94%，其他还包括卵巢外畸胎瘤、肺癌、乳腺癌、睾丸癌、卵巢癌、胸腺癌、胰腺癌等等。Dalmau等[14]对100例抗NMDAR脑炎进行分析，其中58例合并肿瘤，大部分为卵巢畸胎瘤，少数为睾丸畸胎瘤、纵隔畸胎瘤或神经母细胞瘤，而所有畸胎瘤均含有表达NMDAR的神经组织成分。体外研究已证实浸润

于肿瘤的B细胞能够合成抗NMDAR抗体[15]。肿瘤组织NMDAR异位表达刺激机体产生相应的自身抗体，在血脑屏障通透性增加的情况下进入中枢神经系统[16]，抗体与受体相互交联后，导致NMDAR功能的损害[17-19]。对于不合并肿瘤的患者，有学者认为可能与机体的免疫反应造成的肿瘤清除[20]或肿瘤过小[6]不易被现有影像学检查所发现有关。抗NMDAR脑炎与肿瘤如此密切的关系，让我们开始怀疑本例是否也存在类似情况。尤其是刚入院时主诉至今未曾出现月经来潮，使人不由得联想到生殖系统肿瘤的可能。

该患者存在女性生殖器外观幼稚，无阴毛，乳房未发育，早期盆腔磁共振增强扫描及彩超检查提示子宫及卵巢等内在生殖器官缺如，行染色体核型分析发现为46,XY，于是进一步彩超探查腹股沟处发现隐睾，故诊断46,XY DSD。DSD临床分类包括46,XX DSD、46,XY DSD和性染色体型DSD(Klinefelter综合征、特纳综合征、混合性性腺发育不全、嵌合型性腺发育不全)等[21]。本例性激素化验提示睾酮降低，但LH和FSH偏高，说明并非垂体功能不全引起，而是睾丸本身病变造成，可能是分泌睾酮的sertoli和leydig细胞异常。46,XY DSD若残存发育异常的睾丸，随着年龄的增长可能演变为恶性肿瘤，最常见的是性腺母细胞瘤和精原细胞瘤[22]。睾丸位于腹股沟或腹部是恶变的独立危险因素[23]，而抗NMDAR脑炎又常与生殖系统肿瘤相关，故须高度怀疑两者之间存在密切相关。许多学者认为，一旦确诊DSD，应当早期积极切除双侧性腺以防止性腺肿瘤发生[22]，因此治疗期间曾积极建议手术切除发育不良的睾丸，但家属拒绝，这也是本病例缺乏最终病理证据而略显遗憾。但是，根据既往研究证据结合本例特点，我们完全可认为该患者同时存在DSD与自身免疫性脑炎并非巧合，可能存在一定的相关性，大致可能的过程是：DSD出现性腺细胞分化异常，相关抗原的暴露诱发自身免疫抗体(抗NMDAR抗体)的形成，最后通过血脑屏障作用于中枢神经系统的受体(NMDAR)，导致自身免疫性脑炎。当然，这个推论需要后期更多类似患者的报道进一步证实。

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(收稿日期：2022-05-23)
(校对编辑：阮　靖)