论著·临床研究

成人脑型肾上腺脑白质营养不良的临床及遗传学特征

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［摘要］**目的**·探究成人脑型肾上腺脑白质营养不良（adult cerebral adrenoleukodystrophy，ACALD）患者的临床及遗传学特点。**方法**·收集2018年6月至2022年9月在上海交通大学医学院附属第六人民医院就诊的8例ACALD患者的临床资料，包括发病年龄、病程、家族史、现病史及详细的体格检查等结果。影像学检查包括头颅及颈、胸椎磁共振成像（magnetic resonance imaging，MRI）。实验室检测包括血清极长链脂肪酸（very-long-chain fatty acids，VLCFA）、肾上腺皮质功能及基因检测。使用简易精神状态检查量表（Mini-Mental State Examination，MMSE）及蒙特利尔认知评估量表（Montreal Cognitive Assessment，Moca）评估患者的认知功能。**结果**·共纳入8例ACALD患者，均为男性，发病年龄（32.75±5.80）岁（23~40岁），病程4~59个月。患者首发症状差异较大，其中3例患者表现为记忆力下降、认知功能障碍，2例表现为脾气暴躁、易怒、性格改变，1例表现为精神、行为异常，1例表现为构音不清、共济失调，1例表现为持续性头晕、枕部麻木、失眠。5例患者头发稀疏，4例皮肤色素沉着。患者均有多发性脑白质脱髓鞘病灶，以顶枕叶及胼胝体压部等后部白质脱髓鞘模式最常见；3例头颅增强MRI显示部分病灶斑片状强化；2例患者磁共振波谱成像检查均提示胆碱（Cho）峰升高，N-乙酰基天门冬氨酸（NAA）峰减低。6例患者接受血清VLCFA检查，均表现为C26、C24/C22及C26/C22水平升高；7例患者进行肾上腺皮质功能检测，其中6例出现肾上腺皮质功能减退。6例患者有认知功能受损，其中4例患者MMSE及MoCA评分下降，2例患者因严重的认知障碍不能配合评估。共发现8种*ABCD1*基因突变，其中c.1750delC（p.H584Tfs*52）及c.160_170delACGCAGGAGGC（p.T54Lfs*137）为新发现的突变。**结论**·ACALD首发症状多样，以记忆力下降及认知功能障碍最常见。白质脱髓鞘常累及顶枕叶、胼胝体压部，影像学异常早于明显的神经系统症状。头发稀疏、皮肤色素沉着是该病重要特征。血清VLCFA升高及肾上腺皮质功能减退是特征性实验室指标异常。*ABCD1*基因的错义突变常见，1号和6号外显子是中国人热点突变外显子。

［关键词］肾上腺脑白质营养不良；遗传性疾病；X连锁；认知障碍；脱髓鞘疾病；肾上腺功能减退
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Clinical and genetic characteristics of adult cerebral adrenoleukodystrophy

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[Abstract] Objective·To summarize and analyze the clinical and genetic characteristics of adult cerebral adrenoleukodystrophy (ACALD). **Methods**·The data of eight patients with ACALD who attended the Shanghai Sixth People′s Hospital, Shanghai Jiao Tong University School of Medicine from June 2018 to September 2022 were collected and comprehensively analyzed. Clinical data included age at onset, duration of disease, family history, present history and physical examination. Imaging examinations included magnetic resonance imaging (MRI) of the cranial, cervical spine and thoracic spine. Laboratory tests included serum very-long-chain fatty acids (VLCFA), adrenal cortical function and genetic test. Mini-Mental State Examination (MMSE) and Montreal Cognitive Assessment (Moca) were used to assess patients′ cognitive function. **Results**·A total of 8 male patients with ACALD were included in this study. Ageat onset ranged from 23 to 40 years old with an average age of (32.75±5.80) years, and the disease duration ranged from 4 to 59 months. Patients′ first symptoms were highly variable. Three patients showed memory loss and cognitive dysfunction, two showed irritability and personality change, one showed mental and behavioral abnormalities, one showed dysarthria and ataxia, and one showed persistent dizziness, occipital numbness and insomnia. All the patients had multiple white

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matter demyelination lesions, and white matter demyelination in parietal occipital lobe and posterior corpus callosum was the most common. Enhancement MRI showed patchy Gd-enhancement of partial lesions in three cases. In two patients, magnetic resonance spectroscopy showed that choline (Cho) peak increased and N-acetyl-aspartate (NAA) peak decreased. Serum VLCFA levels of C26, C24/C22 and C26/C22 were elevated in six patients who underwent serum VLCFA examination. Seven patients underwent adrenal cortical function testing, of which six experienced adrenal cortical dysfunction. Six patients were cognitively impaired, four of whom had decreased MMSE and MoCA scores, and two of whom were unable to cooperate with the assessment due to severe cognitive impairment. Eight different *ABCD1* gene mutations were identified, among which c.1750delC (p.H584Tfs*52) and c.160_170delACGCAGGAGGC (p.T54Lfs*137) were novel mutations. **Conclusion·**The initial symptoms of ACALD vary, among which memory loss and cognitive dysfunction are the most common. White matter demyelination lesions in the parietal and corpus callosum pressure are the most common, and imaging abnormalities precede neurological symptoms. The clinical features of the disease are hair thinning and skin pigmentation, and the biochemical features are elevated serum VLCFA and adrenal insufficiency. Missense mutations are more common in the *ABCD1* gene, and exons 1 and 6 are the hot mutant exons in Chinese.

[Key words] adrenoleukodystrophy(ACALD); genetic diseases; X-linked; cognition disorders; demyelinating diseases; adrenal insufficiency

肾上腺脑白质营养不良（adrenoleukodystrophy，ALD）是常见的X-连锁隐性遗传的过氧化物酶体疾病。1994年MOSSER等[1]发现该病的致病基因为ATP结合盒转运蛋白超家族成员1（ATP-binding cassette sub-family D，Member 1，*ABCD1*），其编码的肾上腺脑白质营养不良蛋白（adrenoleukodystrophy protein，ALDP）负责将体内循环中酰基化的极长链脂肪酸（very-long-chain fatty acids，VLCFA）转移至过氧化物酶体内进行β氧化分解。因此，当*ABCD1*发生突变时，会导致VLCFA在组织中堆积而致病。该病临床异质性大，从儿童至成人均可发病。按照起病形式，主要分型为脑型ALD（cerebral ALD，CALD）、肾上腺脊髓神经病（adrenomyeloneuropathy，AMN）、单纯Addison病型和女性携带者。临床以儿童脑型ALD（childhood cerebral ALD，CCALD）最多见，占ALD的35%~45%[2]。而成人期起病的ALD患者多表现为缓慢进展的步态异常及括约肌功能障碍等AMN症状[2]。目前，对成人脑型ALD（adult cerebral ALD，ACALD）的临床及遗传特征报道较少。故本研究对8例ACALD患者的临床和遗传学特点进行总结，以提高临床医师对ACALD的认识，提升其对该病的早期诊断能力。

1　对象与方法

1.1　病例收集

收集2018年6月至2022年9月就诊于上海交通大学医学院附属第六人民医院神经内科的ACALD患者的临床资料。病例纳入标准：① 发病年龄>21岁。② 首发症状表现为脑部受累，包括认知功能障碍、精神异常、性格或脾气改变、共济失调等，伴或不伴下肢运动功能异常。③ 头颅磁共振成像（magnetic resonance imaging，MRI）检查发现脑白质脱髓鞘病灶，且Loes评分≥1分。④ 基因检测发现*ABCD1*基因变异。排除其他原因引起的上述神经功能异常。

1.2　基本资料收集

收集患者的临床资料（包括发病年龄、病程、家族史、现病史及脱发、皮肤颜色变化情况等）、影像学检查结果（包括头颅及颈、胸椎MRI）、神经系统查体结果、实验室检查结果（包括血清VLCFA水平、肾上腺皮质功能、脑脊液等）。

1.3　认知功能评估

由经过培训的神经内科医师，采用简易精神状态检查量表（Mini-Mental State Examination，MMSE）及蒙特利尔认知评估量表（Montreal Cognitive Assessment，MoCA）评估患者的认知功能。其中MMSE评分包括定向力、记忆力、注意力和计算力、回忆能力、语言能力5个方面；MoCA评分包括执行功能、语言流畅性、定向力、计算、抽象思维、延迟回忆、视知觉和注意8个维度，2个评分量表总分均为30分。患者每项回答正确得1分，回答错误或不知道得0分。所有患者的受教育年限均>12年，故MMSE得分≤24分和/或MoCA得分<26分评定为认知功能障碍。

1.4　基因检测

取得所有患者及其家属的知情同意后，抽取肘静脉抗凝血3 mL。对先证者样本进行建库和全外显子

组测序，并用一代测序对患者及其家系成员进行共分离验证。

2 结果

2.1 临床特征

共纳入8例患者，均为男性，来自不同家庭；其中6例为散发，2例有家族史。患者发病年龄（32.75±5.80）岁（23~40岁），病程4~59个月。患者首发症状差异较大，3例患者表现为记忆力下降、认知功能障碍，2例表现为脾气暴躁、易怒、性格改变，1例表现为精神、行为异常，1例表现为构音不清晰、共济失调，1例表现为持续性头晕、枕部麻木、失眠。其中1例患者发病前有头部外伤史，2例患者受情感打击，5例患者无明确发病诱因。5例患者头发稀疏，4例患者皮肤色素沉着。就诊时，6例患者出现步态不稳、走路姿势异常，其中5例因严重的步态异常需依赖拐杖或轮椅。6例患者有不同程度的认知功能受损，其中4例患者（P1、P5、P6、P7）的MMSE/MoCA评分分别为21/17、21/16、14/9、23/16，2例患者（P3、P8）因严重的认知障碍不能配合评估（表1）。3例患者球部症状明显，表现为言语含糊、饮食水呛咳，2例患者有癫痫发作，3例患者出现小便急、尿失禁，2例患者大便失禁。神经系统阳性体征主要有5例下肢肌张力升高，6例下肢反射亢进，3例踝阵挛（+），5例病理征（+）。

表1 ACALD患者基本信息、临床特征及实验室指标

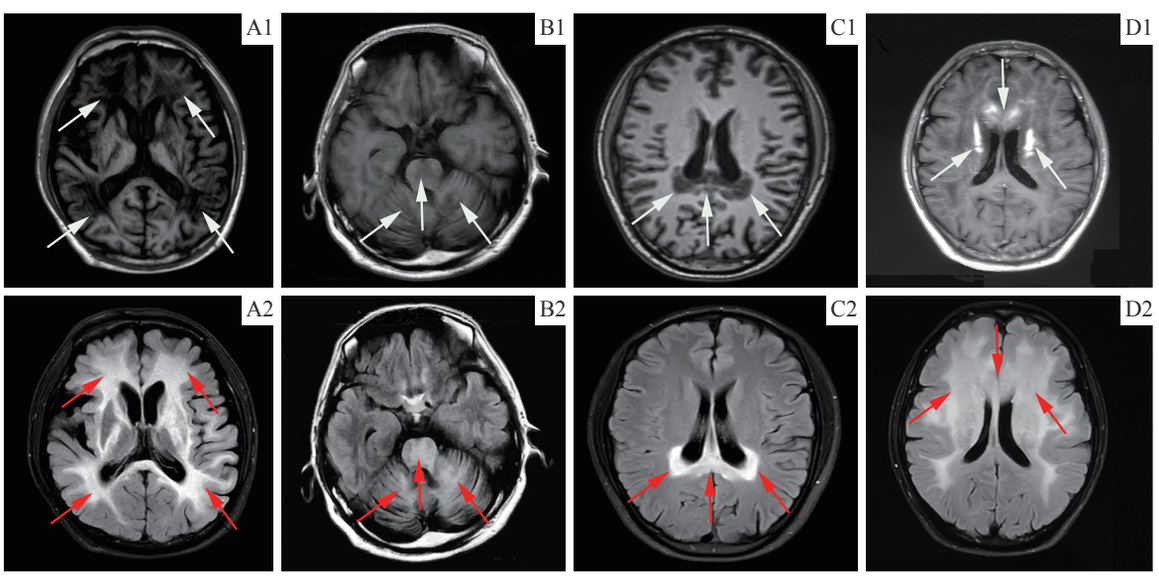
Tab 1 General information, and clinical and biochemical characteristics of ACALD patients

Items	P1	P2	P3	P4	P5	P6	P7	P8
Age of onset/Years	27	23	40	37	34	30	33	38
Disease duration/Months	12	4	59	31	5	4	8	16
First symptoms	Memory and cognitive decline	Dizziness with occipital numbness, insomnia	Mental and behavioral abnormalities	Dysarthria and ataxia	Bad temper, personality change	Memory and cognitive decline	Memory decline	Bad temper, personality change
MMSE/MoCA	21/17	ND	NA	ND	21/16	14/9	23/16	NA
VLCFA								
C26(≤1.30 nmol/mL)	5.71	ND	3.94	ND	3.77	3.03	3.28	3.38
C24/C22(≤1.39)	1.89	ND	1.50	ND	1.46	1.77	1.76	1.95
C26/C22(≤0.023)	0.132	ND	0.065	ND	0.077	0.068	0.070	0.073
Adrenal insufficiency								
Cortisol levels	↓	ND	↓	↓	N	N	↓	↓
ACTH	↑	ND	↑	↑	N	↑	↑	↑
Protein content in cerebrospinal fluid	1.00 g/L	N	0.47 g/L	0.47 g/L	N	ND	ND	ND
Mutation information								
Exon	8	10	6	7	1	1	6	3
Nucleotide mutations	c.1817C>T	c.2135G>A	c.1559T>C	c.1750delC	c.323C>T	c.160_170delACGCAGGAGGC	c.1534G>A	c.1202G>A
Amino acid variants	S606L	R712H	L520P	H584Tfs*52	S108L	T54Lfs*137	G512S	R401Q
ACMG	Pathogenic	VUS	VUS	Pathogenic	Pathogenic	Pathogenic	Pathogenic	Pathogenic
Reported phenotypes	CCALD[3], AMN[4],AO[5]	NB[6]	NB[6]	–	CCALD[7], AO[8], AMN[9], Olivo-ponto-cerebellar[10]	–	CCALD[11], AMN[12], ACALD[11], AO[13], Female[14]	CCALD[7], AMN[15], ACALD[16], NB[6]AO[17], Female carrier[18]

Note: N—normal; NA—not available; ND—not done; VUS—variants of uncertain significance; AO—addison only; NB—newborn screening; ACMG—Association of Canadian Mountain Guides.

2.2　影像及实验室检查

所有患者均进行了头颅MRI检查（图1），均有多发性脑白质脱髓鞘病灶。其中5例患者（P1、P2、P5、P6、P7）表现为顶枕叶及胼胝体压部的后部白质脱髓鞘模式；1例患者（P4）表现为小脑白质脱髓鞘；1例患者（P8）表现为额顶颞叶及胼胝体膝部的前部白质脱髓鞘模式；1例晚期患者（P3）出现弥漫性白质脱髓鞘。3例患者行头颅增强MRI扫描，均显示部分病灶斑片状强化。3例患者颈胸椎MRI检查均未见异常。2例患者（P1、P5）行磁共振波谱成像检查均提示胆碱（choline，Cho）峰升高，N-乙酰基天门冬氨酸（N-acetyl-L-aspartic acid，NAA）峰减低。4例患者行脑电图检查，其中2例有癫痫发作的患者（P3、P8）脑电波异常，表现为中度异常成人清醒期脑电图和中度异常脑电图，双侧额、前中颞区慢波，右侧额、前中颞区负荷棘慢波。6例患者血清VLCFA检查，均表现为血清C26、C24/C22及C26/C22水平升高。7例患者进行肾上腺皮质功能检测，6例患者出现肾上腺皮质功能减退，需口服氢化可的松替代治疗，患者血清促肾上腺皮质激素（ACTH）均升高，其中5例血清皮质醇水平下降，1例血清皮质醇水平正常。5例患者行腰椎穿刺检查，其中3例患者脑脊液蛋白轻度升高，常规检查正常。



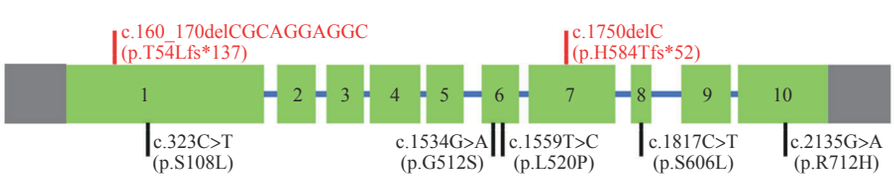
Note: A. Advanced ACALD patient (P3), extensive and diffuse distribution of white matter lesions with typical butterfly wing-like changes. B. Olivopontocerebellar ACALD patient (P4), white matter demyelinating lesions involving the bilateral cerebellar hemispheres and brainstem. C. Early stage ACALD patient (P5), white matter demyelinating lesions involving the posterior horn of the lateral ventricle and the corpus callosum. D. Rapidly progressive ACALD patient (P8), white matter demyelination lesions involving the anterior horn of the lateral ventricle and the anterior part of the white matter in the frontotemporal lobe. Some lesions showed patchy enhancement on the T1 enhanced sequence (D1, white arrow). Patients with ACALD had bilateral symmetrical cerebral white matter demyelinating lesions with low signal in T1 sequences (white arrows in A1-C1) and high signal in FLAIR sequences (red arrows in A2-D2).

图1　ACALD患者头颅MRI

Fig 1　Cranial MRI of ACALD patients

2.3　遗传学分析

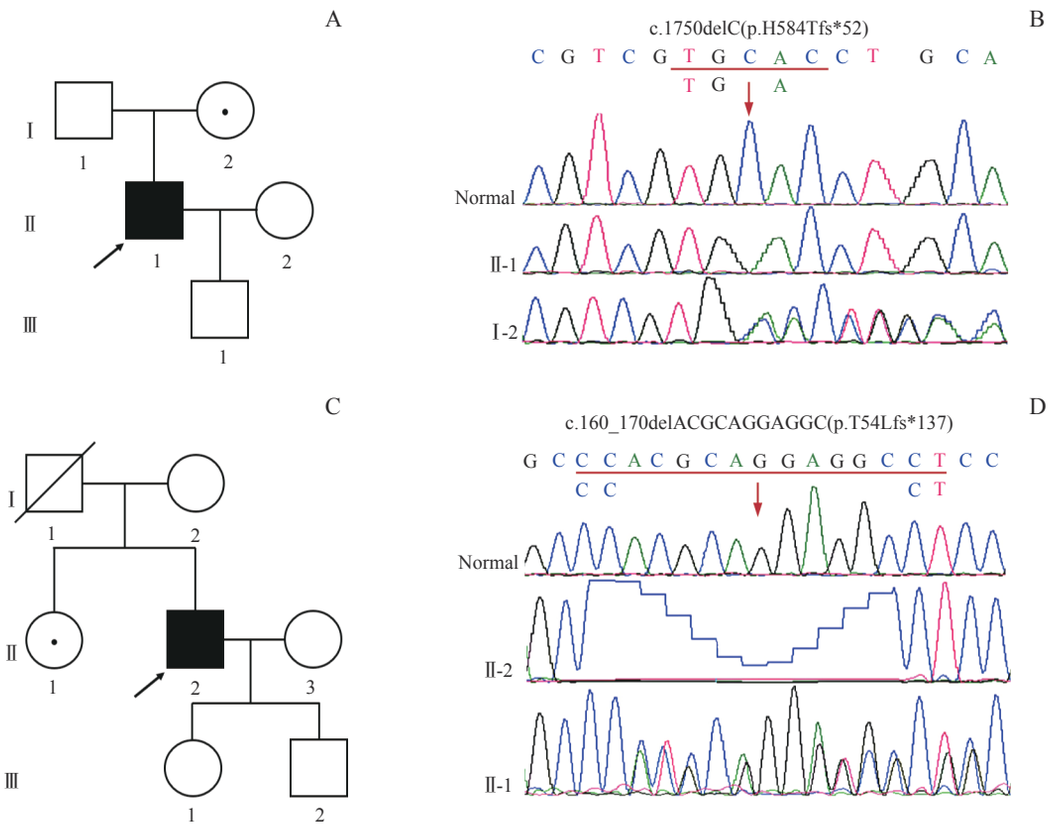
8例患者均进行了基因检测，发现了8种不同的*ABCD1*基因突变（表1，图2），包括6种错义突变、2种移码突变。1和6号外显子各2例，3、7、8、10号外显子各1例。其中，c.1750delC（p.H584Tfs*52）及c.160_170delACGCAGGAGGC（p.T54Lfs*137）未被人类基因突变数据库收录，为新发现的突变（图3）。



Note: Red indicates new mutations reported in this study. Black indicates previously reported mutations.

图2　ACALD患者*ABCD1*基因突变示意图

Fig 2　Schematic diagram of *ABCD1* gene mutation in ACALD patients



Note: A. Pedigree of patient P4. B. The proband P4 was Hemizygous for c.1750delC, and his mother was Heterozygous at this site (red arrow). C. Pedigree of patient P6. D. The proband P6 was Hemizygous for c.160_170delACGCAGGAGGC, and his elder sister was Heterozygous at this site (red arrow). The rest of the family refused to have blood drawn, so the genetic results were not verified.

图3　患者家系图及Sanger测序图

Fig 3　Pedigree and Sanger sequencing of ACALD patients

3　讨论

ALD临床异质性大。在国外的报道中，CALD主要累及儿童，而ACALD则较罕见，占ALD的2%~5%[19]。在国内，CCALD较国外报道更多，约占本病的80%[20]，ACALD仅占3.3%或更少[3,21]。相较于儿童患者早期突出的学习障碍和行为问题，以及迅速的病程进展，临床上ACALD患者早期症状隐匿且首发症状表现多样，病程进展差异性大。认知功能障碍和精神行为异常是ACALD最常见的早期表现形式，尤其是当病变位于额叶时，患者症状类似于抑郁症或精神疾病[22]。在疾病的早期，精神行为异常可能是患者唯一的症状，而无神经系统阳性体征[23]。头部外伤及手术是诱发和加重病情的外部因素[24-25]，多发生在3~12个月后。本研究中患者P7发病12个月前有明确的头部外伤史，但与既往报道[25]不同，该患者脱髓鞘部位与脑挫伤部位不一致。此外，患者P2和P3在发病前遭受情感打击。目前，尚无精神创伤诱发ALD发病的报道。精神创伤是否为发病的触发因素及其具体机制，需要更多的研究证实。本研究中，患者的发病年龄为（32.75±5.80）岁。目前，国内外尚无ACALD患者发病年龄的统计。但与AMN患者发病年龄［（27.6±8.7）岁］比较，ACALD患者发病稍晚[26]。早期部分患者症状不典型，随着病情的进展，多数患者会出现疾病的各种症状[19]，可能出现锥体束征及中枢性视觉异常，部分患者会有癫痫发作。本研究中，6例患者除有脑部受累的症状外，还表现为步态异常，其中5例患者需拐杖或轮椅助行。此外，本研究中的1例为罕见的橄榄脑桥小脑型ALD，其特征是头颅MRI表现为累及小脑和脑干脱髓鞘病变，临床主要表现为小脑共济失调、步态异常和语言障碍。此类患者常伴有假性球麻痹的症状，病程进展差异性大，患者生存期为3年到30余年不等；疾病的晚期，患者多死于严重的肺部感染[27]。本研究中，患者P4以构音不清、共济失调起病，头颅MRI检查表现为典型的橄榄脑桥小脑型ALD白质

病变模式。发病2年后，患者因严重的共济失调需要依赖轮椅，并有发音障碍及饮水呛咳的症状，病程进展较快。目前，全球所报道的病例主要分布在韩国、日本等亚洲地区[27-29]，约占ALD的8.4%。而在中国大陆和台湾地区，仅有数例小脑型病例报道[29-32]。这可能因为国内对该疾病认识不足，且部分患者病灶隐匿，仅在死后尸检发现小脑及脑干轻度脱髓鞘改变，因此易误诊为多系统萎缩[27]。

头颅MRI特征性病灶有助于疾病的诊断。在疾病早期，患者头颅MRI脱髓鞘病灶最常累及顶枕叶、胼胝体压部白质，双侧对称融合，呈蝶翼样外观，在T1序列呈低信号，在T2及液体衰减反转恢复（fluid attenuated inversion recovery，FLAIR）序列上呈高信号[33]。少数患者最初表现为额顶叶及胼胝体膝部白质脱髓鞘的前部受累模式。随着病情的进展，在疾病晚期，白质广泛受累，脱髓鞘病灶呈弥漫性分布。本研究中，5例患者早期表现为典型的后部白质脱髓鞘模式。其中，P2就诊时处于疾病的早期，首发症状为持续性头晕、枕部麻木不适、失眠等非特异性改变，患者认知及行为正常，头颅MRI检查发现脑室旁多发白质脱髓鞘病灶，符合遗传代谢性脑白质病的影像学特征，最终经全外显子测序发现*ABCD1*基因突变而确诊为ALD。与既往报道一致[34]，患者头颅MRI脱髓鞘改变多出现在明显的认知及行为异常之前。患者P3发病59个月时首次就诊于我院，此时已处于疾病的晚期，出现脑白质弥漫性脱髓鞘改变。此外，MRI增强检查发现病灶周围钆增强与活动性炎症脱髓鞘有关，是预后不良的表现[35]。磁共振波谱成像是一种非侵入性的观察活体组织代谢变化的成像技术，通过不同的波峰及其峰值的大小反映组织内各化学物质的含量。其中，NAA仅表达于神经细胞中，其峰值的大小反映了神经元的功能状况；Cho是细胞膜磷脂代谢的成分之一，其峰值在脑恶性肿瘤及急性脱髓鞘疾病中升高[36]。本研究，患者P1和P5的磁共振波谱成像检查均观察到了Cho峰升高及NAA峰减低，这说明在脑型CALD患者中，同时存在白质脱髓鞘和神经元的损伤。

VLCFA指由22个或者更多碳原子组成的脂肪酸。正常情况下，从食物中摄取和内源性合成的VLCFA通过β氧化的方式在过氧化物酶体内分解代谢；而在ALD患者中，由于β氧化功能障碍，使其聚积在血液及组织中。因此，几乎在所有的男性患者中均能发现血液中VLCFA水平的升高，尤其是C26及C26/C22不易受饮食及机体应激状态的影响[37]，是筛查ALD的敏感指标。血清VLCFA升高是ALD特征性实验室指标，但VLCFA在ALD发病机制中的作用尚不明确。目前一些体内及体外研究表明，VLCFA可能通过诱导细胞产生氧化应激和炎症的方式导致组织损伤[38]。本研究中6例进行检测的患者中，均发现血清VLCFA升高。但VLCFA水平与患者疾病的严重程度无关，且在不同的ALD类型中，也未发现VLCFA水平的差异[39]。因此，VLCFA水平并不能用于监测疾病的进展。肾上腺皮质功能不全合并脑白质脱髓鞘是该病特征性表现，患者多表现为关节、乳头及牙龈等处的皮肤颜色变黑，厌食和体质量减轻[40]。肾上腺皮质功能不全的终身患病率约为80%，约46.8%出现在小于10岁的儿童中。而在成人中，随着年龄的增长，患病率逐渐下降，仅约5.6%发生在40岁以上的患者中[39]。鉴于肾上腺皮质功能不全的年龄相关性，对于小于40岁的成人患者，应每年检测一次肾上腺皮质功能；在40岁之后，如果出现内分泌系统症状，则可仅按需检测[39]。本研究中，6例患者因肾上腺皮质功能不全需口服氢化可的松治疗。目前，尚无ALD患者何时进行激素替代治疗的统一标准。临床上多在患者出现促肾上腺皮质激素（adrenocorticotropic hormone，ACTH）水平升高伴或不伴有皮质醇降低，或ACTH刺激试验异常（即皮质醇水平升高小于基线水平2倍）时开始口服激素替代治疗。

ALD的发病率约为1∶14 700[41]，*ABCD1*是唯一的致病基因，该基因由10个外显子和9个内含子组成。目前，有3 600余种*ABCD1*基因突变的报道（The ABCD1 Variant Database-Adrenoleukodystrophy.info）。其中，错义突变是最常见的突变类型，约占50.4%；其次为移码突变，约占25.5%。1号外显子是国内外报道的热点突变外显子，约占所有突变的42.0%。本研究的病例中发现了8种不同的变异，其中6个为错义突变，2个为移码突变，与另一项国内报道相似[42]，错义突变的比例均明显高于国外。此外，2个突变位于6号外显子，明显高于全球数据库中的11%，这一结果与之前国内及日本报道一致[43-44]，即6号外显子是亚洲人群的另一个突变聚集区。然而，由于本研究中样本量少，这一结果尚需更多的数据进一步验证。本研究总结了6种已报

道基因突变的表型分布特征，与既往的报道[45]一致，即患者的基因型和表型之间没有明显的相关性，即使在携带相同突变的同卵双生子中，患者也能出现不同的表型。2种突变（c.2135G>A和c.1559T>C）仅在新生儿筛查中发现，本文首次报道了其致病性表型。此外，本研究报道了*ABCD1*基因的2种新的移码突变（c.1750delC及c.160_170delACGCAGGAGGC），突变导致了ALDP翻译的提前终止而致病。

ACALD是一种高致死性疾病，未经治疗的患者平均在发病后7.5年死亡，在疾病早期进行异基因造血干细胞移植是阻止和延缓患者病情进展唯一有效方法[28]。然而对于晚期患者，即Loes评分大于10分、扩展残疾状况量表（Expanded Disability Status Scale，EDSS）评分≥6分[46]、广泛锥体束受累和晚期严重认知障碍的患者[47]，移植并不能提高患者的生存率，早期诊断是挽救患者生命的关键。

利益冲突声明/Conflict of Interests

所有作者声明不存在利益冲突。

All authors disclose no relevant conflict of interests.

伦理批准和知情同意/Ethics Approval and Patient Consent

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All experimental protocols in this study were reviewed and approved by Shanghai Sixth People′s Hospital, Shanghai Jiao Tong University School of Medicine (Approval Letter No. 2021-219, dated 02/19/2021), and all experimental protocols were carried out by following the guidelines of *The Nuremberg Code*. Consent letters have been signed by the research participants or their relatives.

作者贡献/Authors′ Contributions

刘桃桃、张梅、曹立参与了研究设计；刘桃桃、刘晓黎、邬静莹、张梅、曹立参与了论文的写作和修改；刘桃桃、邬静莹、倪瑞隆、张梦圆、季杜欣参与了数据分析。所有作者均阅读并同意了最终稿件的提交。

The study was designed by LIU Taotao, ZHANG Mei and CAO Li. The manuscript was drafted and revised by LIU Taotao, LIU Xiaoli, WU Jingying, ZHANG Mei and CAO Li. The data was analyzed by LIU Taotao, WU Jingying, NI Ruilong, ZHANG Mengyuan, and JI Duxin. All the authors have read the last version of paper and consented for submission.

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参·考·文·献

[1] MOSSER J, LUTZ Y, ELISABETH STOECKEL M, et al. The gene responsible for adrenoleukodystrophy encodes a peroxisomal membrane protein[J]. Hum Mol Genet, 1994, 3(2): 265-271.

[2] JANGOUK P, ZACKOWSKI K M, NAIDU S, et al. Adrenoleukodystrophy in female heterozygotes: underrecognized and undertreated[J]. Mol Genet Metab, 2012, 105(2): 180-185.

[3] 平莉莉, 包新华, 王爱花, 等. X连锁肾上腺脑白质营养不良89例临床特征及基因型/表型关系[J]. 中华儿科杂志, 2007, 45(3): 203-207.
PING L L, BAO X H, WANG A H, et al. Clinical features and genotype-phenotype studies of 89 Chinese patients with X-linked adrenoleukodystrophy[J]. Chinese Journal of Pediatrics, 2007, 45(3): 203-207.

[4] LI J, WANG H, HE Z, et al. Clinical, neuroimaging, biochemical, and genetic features in six Chinese patients with Adrenomyeloneuropathy[J]. BMC Neurol, 2019, 19(1): 227.

[5] WATKINS P A, GOULD S J, SMITH M A, et al. Altered expression of ALDP in X-linked adrenoleukodystrophy[J]. Am J Hum Genet, 1995, 57(2): 292-301.

[6] MATTESON J, SCIORTINO S, FEUCHTBAUM L, et al. Adrenoleukodystrophy newborn screening in California since 2016: programmatic outcomes and follow-up[J]. Int J Neonatal Screen, 2021, 7(2): 22.

[7] LIBERATO A P, MALLACK E J, AZIZ-BOSE R, et al. MRI brain lesions in asymptomatic boys with X-linked adrenoleukodystrophy[J]. Neurology, 2019, 92(15): e1698-e1708.

[8] GUIMARÃES C P, LEMOS M, SÁ-MIRANDA C, et al. Molecular characterization of 21 X-ALD Portuguese families: identification of eight novel mutations in the *ABCD1* gene[J]. Mol Genet Metab, 2002, 76(1): 62-67.

[9] ASHEUER M, BIECHE I, LAURENDEAU I, et al. Decreased expression of *ABCD4* and *BG1* genes early in the pathogenesis of X-linked adrenoleukodystrophy[J]. Hum Mol Genet, 2005, 14(10): 1293-1303.

[10] CHEN Y H, LEE Y C, TSAI Y S, et al. Unmasking adrenoleukodystrophy in a cohort of cerebellar ataxia[J]. PLoS One, 2017, 12(5): e0177296.

[11] OLGAC A, KASAPKARA Ç S, DERINKUYU B, et al. Retrospective evaluation of patients with X-linked adrenoleukodystrophy with a wide range of clinical presentations: a single center experience[J]. J Pediatr Endocrinol Metab, 2021, 34(9): 1169-1179.

[12] GÄRTNER J, BRAUN A, HOLZINGER A, et al. Clinical and genetic aspects of X-linked adrenoleukodystrophy[J]. Neuropediatrics, 1998, 29(1): 3-13.

[13] OZDEMIR KUTBAY N, OZBEK M N, SARER YUREKLI B, et al. A distinct clinical phenotype in two siblings with X-linked adrenoleukodystrophy[J]. Neuro Endocrinol Lett, 2019, 40(1): 36-40.

[14] MAIER E M, KAMMERER S, MUNTAU A C, et al. Symptoms in carriers of adrenoleukodystrophy relate to skewed X inactivation[J]. Ann Neurol, 2002, 52(5): 683-688.

[15] HSU S L, CHEN Y H, CHOU C T, et al. Investigating *ABCD1* mutations in a Taiwanese cohort with hereditary spastic paraplegia phenotype[J]. Parkinsonism Relat Disord, 2021, 92: 7-12.

[16] CHU S S, YE J, ZHANG H W, et al. Eight novel mutations in the *ABCD1* gene and clinical characteristics of 25 Chinese patients with

X-linked adrenoleukodystrophy[J]. World J Pediatr, 2015, 11(4): 366-373.

[17] CAPALBO D, MORACAS C, CAPPA M, et al. Primary adrenal insufficiency in childhood: data from a large nationwide cohort[J]. J Clin Endocrinol Metab, 2021, 106(3): 762-773.

[18] SALSANO E, TABANO S, SIRCHIA S M, et al. Preferential expression of mutant *ABCD1* allele is common in adrenoleukodystrophy female carriers but unrelated to clinical symptoms[J]. Orphanet J Rare Dis, 2012, 7: 10.

[19] KEMP S, HUFFNAGEL I C, LINTHORST G E, et al. Adrenoleukodystrophy-neuroendocrine pathogenesis and redefinition of natural history[J]. Nat Rev Endocrinol, 2016, 12(10): 606-615.

[20] JIA M R, WU W Z, LI C M, et al. Clinical characteristics and phenotype distribution in 10 Chinese patients with X-linked adrenoleukodystrophy[J]. Exp Ther Med, 2019, 18(3): 1945-1952.

[21] 罗晓妹, 刘丽英, 邹丽萍, 等. X-连锁肾上腺脑白质营养不良表型及基因型研究[J]. 中华神经科杂志, 2021, 54(7): 686-692.
LUO X M, LIU L Y, ZOU L P, et al. Study on the phenotype and genotype of X-linked adrenoleukodystrophy[J]. Chinese Journal of Neurology, 2021, 54(7): 686-692.

[22] GARSIDE S, ROSEBUSH P I, LEVINSON A J, et al. Late-onset adrenoleukodystrophy associated with long-standing psychiatric symptoms[J]. J Clin Psychiatry, 1999, 60(7): 460-468.

[23] FURUHASHI Y, ISHIKAWA M. Adult-onset adrenoleukodystrophy heralded by auditory hallucinations and delusions[J]. Psychosomatics, 2011, 52(5): 492-493.

[24] BOUQUET F, DEHAIS C, SANSON M, et al. Dramatic worsening of adult-onset X-linked adrenoleukodystrophy after head trauma[J]. Neurology, 2015, 85(22): 1991-1993.

[25] BUDHRAM A, PANDEY S K. Activation of cerebral X-linked adrenoleukodystrophy after head trauma[J]. Can J Neurol Sci, 2017, 44(5): 597-598.

[26] MOSER H W, MOSER A B, SMITH K D, et al. Adrenoleukodystrophy: phenotypic variability and implications for therapy[J]. J Inherit Metab Dis, 1992, 15(4): 645-664.

[27] OGAKI K, KOGA S, AOKI N, et al. Adult-onset cerebello-brainstem dominant form of X-linked adrenoleukodystrophy presenting as multiple system atrophy: case report and literature review[J]. Neuropathology, 2016, 36(1): 64-76.

[28] MATSUKAWA T, YAMAMOTO T, HONDA A, et al. Clinical efficacy of haematopoietic stem cell transplantation for adult adrenoleukodystrophy[J]. Brain Commun, 2020, 2(1): fcz048.

[29] YAN F, WANG W, YING H, et al. S149R, a novel mutation in the *ABCD1* gene causing X-linked adrenoleukodystrophy[J]. Oncotarget, 2017, 8(50): 87529-87538.

[30] 梁凯, 梁建华, 马红玲. 以小脑脑干为突出表现的成人型X-连锁肾上腺脑白质营养不良症一例[J]. 中华神经科杂志, 2018, 51(9): 738-742.
LIANG K, LIANG J H, MA H L. One case of adult X-linked adrenoleukodystrophy characterized by cerebellar symptoms. [J]. Chinese Journal of Neurology, 2018, 51(9): 738-742.

[31] LI J Y, HSU C C, TSAI C R. Spinocerebellar variant of adrenoleukodystrophy with a novel *ABCD1* gene mutation[J]. J Neurol Sci, 2010, 290(1/2): 163-165.

[32] 王梦文, 伍楚君, 张在强. 成年肾上腺脑白质营养不良患者临床及遗传分析[J]. 罕见病研究, 2022(2): 130-136.
WANG M W, WU C J, ZHANG Z Q. Clinical and genetic analysis of adrenoleukodystrophy in adults[J]. Journal of Rare Diseases, 2022(2): 130-136.

[33] SCHIFFMANN R, VAN DER KNAAP M S. Invited article: an MRI-based approach to the diagnosis of white matter disorders[J]. Neurology, 2009, 72(8): 750-759.

[34] BUERMANS N J M L, VAN DEN BOSCH S J G, HUFFNAGEL I C, et al. Overall intact cognitive function in male X-linked adrenoleukodystrophy adults with normal MRI[J]. Orphanet J Rare Dis, 2019, 14(1): 217.

[35] KIM J H, KIM H J. Childhood X-linked adrenoleukodystrophy: clinical-pathologic overview and MR imaging manifestations at initial evaluation and follow-up[J]. Radiographics, 2005, 25(3): 619-631.

[36] VAN DE STADT S I W, SCHRANTEE A, HUFFNAGEL I C, et al. Magnetic resonance spectroscopy as marker for neurodegeneration in X-linked adrenoleukodystrophy[J]. Neuroimage Clin, 2021, 32: 102793.

[37] STRADOMSKA T J, BACHAŃSKI M, PAWŁOWSKA J, et al. The impact of a ketogenic diet and liver dysfunction on serum very long-chain fatty acids levels[J]. Lipids, 2013, 48(4): 405-409.

[38] YU J, CHEN T, GUO X, et al. The role of oxidative stress and inflammation in X-link adrenoleukodystrophy[J]. Front Nutr, 2022, 9: 864358.

[39] HUFFNAGEL I C, LAHEJI F K, AZIZ-BOSE R, et al. The natural history of adrenal insufficiency in X-linked adrenoleukodystrophy: an international collaboration[J]. J Clin Endocrinol Metab, 2019, 104(1): 118-126.

[40] DONG B, LV W, XU L, et al. Identification of two novel mutations of *ABCD1* gene in pedigrees with X-linked adrenoleukodystrophy and review of the literature[J]. Int J Endocrinol, 2022, 2022: 5479781.

[41] VAN ROERMUND C W, VISSER W F, IJLST L, et al. The human peroxisomal ABC half transporter ALDP functions as a homodimer and accepts acyl-CoA esters[J]. FASEB J, 2008, 22(12): 4201-4208.

[42] PEREIRA FDOS S, MATTE U, HABEKOST C T, et al. Mutations, clinical findings and survival estimates in South American patients with X-linked adrenoleukodystrophy[J]. PLoS One, 2012, 7(3): e34195.

[43] SHIMOZAWA N, HONDA A, KAJIWARA N, et al. X-linked adrenoleukodystrophy: diagnostic and follow-up system in Japan[J]. J Hum Genet, 2011, 56(2): 106-109.

[44] NIU Y F, NI W, WU Z Y. *ABCD1* mutations and phenotype distribution in Chinese patients with X-linked adrenoleukodystrophy [J]. Gene, 2013, 522(1): 117-120.

[45] KORENKE G C, FUCHS S, KRASEMANN E, et al. Cerebral adrenoleukodystrophy (ALD) in only one of monozygotic twins with an identical ALD genotype[J]. Ann Neurol, 1996, 40(2): 254-257.

[46] KÜHL J S, SUAREZ F, GILLETT G T, et al. Long-term outcomes of allogeneic haematopoietic stem cell transplantation for adult cerebral X-linked adrenoleukodystrophy[J]. Brain, 2017, 140(4): 953-966.

[47] WALDHüTER N, KöHLER W, HEMMATI PG, et al. Allogeneic hematopoietic stem cell transplantation with myeloablative conditioning for adult cerebral X-linked adrenoleukodystrophy [J]. J Inherit Metab Dis, 2019, 42(2):313-324.

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