

doi: 10.13241/j.cnki.pmb.2014.28.017

· 临床研究 ·

常染色体显性多囊肾病合并颅内动脉瘤的临床特征
及其随访研究*肖燎原^{1,2} 盛 珺² 郁胜强² 王 鹏² 梅长林^{2△}

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摘要 目的:探讨常染色体显性多囊肾病(Autosomal dominant polycystic kidney disease, ADPKD)合并颅内动脉瘤的临床特征及其预后情况。**方法:**选择 355 例 2007 年 11 月至 2008 年 11 月上海长征医院收治的被诊断为 ADPKD 的患者为研究对象,分析其临床资料及头部动脉瘤 MRA 筛查的结果,并对合并颅内动脉瘤的患者进行随访。**结果:**355 例 ADPKD 患者颅内动脉瘤的发病率为 12.4%,发病率随年龄的增加而升高,60-69 岁组的发病率为 23.3%,有脑卒中家族史的患者发病率明显高于无明确脑卒中家族史的患者($P<0.05$)。大部分动脉瘤较小(平均直径 $3.85\pm 3.25\text{mm}$),且都位于前循环,其中颈内动脉最常见(占 48.1%)。对 44 位合并颅内动脉瘤的患者进行随访,共随访 21 位患者(27 枚动脉瘤),平均随访 43.5 ± 4.3 月,未发现新生动脉瘤;2 枚动脉瘤有明显增大,扩大率为 7.4%,其余 25 枚动脉瘤无明显增大,无动脉瘤破裂。**结论:**年龄 ≥ 30 岁和具有脑卒中家族史的 ADPKD 患者易并发颅内动脉瘤,大多直径较小且位于前循环,随访期间大多无明显增大或破裂。

关键词:常染色体显性多囊肾病;颅内动脉瘤;筛查;随访

中图分类号:R692.1 文献标识码:A 文章编号:1673-6273(2014)28-5468-05

Observation on the Clinical Characteristics and Follow-up of Autosomal Dominant Polycystic Kidney Combined with Intracranial Aneurysms*

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ABSTRACT Objective: To investigate the clinical characteristics and prognosis of autosomal dominant polycystic kidney disease (ADPKD) with intracranial aneurysm (ICA). **Methods:** Patients who were diagnosed as ADPKD from November 2007 to November 2008 in CHANG ZHENG hospital were selected as research objects. Their clinical data and MRI data were collected and analyzed, and patients with ICA were followed up (recheck MRI and collect clinical data). **Results:** 355 patients with ADPKD were found. The incidence rate was 12.4%, which increased as the age increased, reaching a peak value of 23.3% in the 60-69 year age group. The incidence rate of ICA in patients with ADPKD with a positive family history of hemorrhagic stroke was higher than that lack such family history ($P<0.05$). Most aneurysms were small (median diameter $3.85\pm 3.25\text{ mm}$) and all in the anterior circulation, the most common location was in internal carotid artery (48.1%). 21 patients, 27 aneurysms had imaging follow-up. During cumulative imaging follow-up of 43.5 ± 4.3 months, no de novo ICA was detected and two ICA grew obviously with enlargement rate was 7.4%. No evident change was detected in the remaining 25 aneurysms, no aneurysm ruptured. **Conclusion:** Patients whose age were older than 30 or had family history of hemorrhagic stroke were pretended to suffer from ICA. Most ICAs were small and located in the anterior circulation, during the duration of followed-up, the majority of ICA hadn't enlarged and ruptured.

Key words: ADPKD; ICA; Screening; Follow-Up

Chinese Library Classification(CLC): R692.1 **Document code:** A

Article ID: 1673-6273(2014)28-5468-05

* 基金项目:上海市科委重点科技攻关项目(11431920800)

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(收稿日期:2014-04-05 接受日期:2014-04-28)

前言

常染色体显性多囊肾病(ADPKD)是一种常见的累及多系统的单基因遗传病,(约 800-1000 人中有一人发病),以肾囊肿扩大和肾功能进行性恶化为特征,肾外表现主要包括高血压、多囊肝和颅内动脉瘤。与正常人群比较,ADPKD 患颅内动脉瘤的危险性显著增加,流行病学调查约为 8%,是正常人 5 倍左右^[1];ADPKD 颅内动脉瘤破裂致蛛网膜下腔出血的危险性较正常人群明显升高,一旦破裂会造成约 30-40%死亡率,另外 30%会留下严重的后遗症,危害大。因此,筛查 ADPKD 患者的颅内动脉瘤和对已发现的颅内动脉瘤患者的复查很重要。本研究旨在通过头部 MRI 筛查、随访和临床随访来评价 ADPKD 合并 ICA

患者动脉瘤大小变化和破裂危险因素及临床特点,并为动脉瘤的是否要复查以及复查时机的把握提供依据。

1 资料与方法

1.1 病人来源

选择 2007 年 11 月到 2008 年 11 月在中国第二军医大学长征医院肾内科被诊断为 ADPKD 的 378 例患者,诊断标准为腹部超声或 CT 发现双肾囊肿数 ≥ 5 , 常有明确的多囊肾病家族史。除 23 例患者拒绝参与外,其余 355 名患者均进行头部 MRI 筛查,其中男性 186 例,女性 169 例,来自 288 个家族,平均年龄 46.5 ± 13.2 岁(7~87 岁),患者的一般资料见表 1。

表 1 355 例 ADPKD 患者的一般资料
Table 1 General data of 355 patients with ADPKD

	Participants(n_355)	Patients With ICAN(n=44)
Mean age $\pm$ SD, years	46.5 $\pm$ 13.2	52.6 $\pm$ 10.6
≤ 29 years	42	1
30-39years	67	4
40-49years	80	9
50-59years	114	19
60-69years	43	10
≥ 70 years	9	1
Women	169	23
Mean duration of ADPKD_SD, years	10.5 $\pm$ 8.4	12.2 $\pm$ 8.0
Family history with positive hemorrhagic stroke or ICAN	51	11
Family history with possible hemorrhagic stroke or ICAN	12	1
Family history with negative hemorrhagic stroke or ICAN	292	32
Renal dysfunction	112	17
Hypertension	249	32
Liver cyst	216	29

1.2 动脉瘤的评价标准

新生动脉瘤:原先检查无动脉瘤的位置发现直径 ≥ 1 mm 的动脉瘤;动脉瘤增大:动脉瘤平均直径增大的幅度 ≥ 1 mm。随访时间:两次 MRI 筛查间隔时间。

1.3 统计学分析

所有数据用 SPSS 18 统计软件处理,患病率计算 95%可信区间,所有定量资料和定性资料分别用方差分析和卡方检验,危险因素分析采用 Logistic 回归分析,以 $P < 0.05$ 为差异有统计学意义。

2 结果

2.1 患者的一般资料

共 355 例 ADPKD 患者接受了 MRI 筛查,平均年龄为 46.5 ± 13.2 岁;其中 51 例(14.4%)有明确蛛网膜下腔出血家族史(SAH)或颅内动脉瘤家族史,292 例(82.3%)无 SAH 或 ICA 家族史,12 例(3.3%)SAH 或 ICA 家族史不明确;249 例(70.1%)

患高血压;216 例(60.8%)合并多囊肝;112 例(31.5%)肾功能不全。来自 38 个家族的 44 位患者(23 位女性,21 位男性)筛查发现患有 ICA,诊断时患者的平均年龄 52.6 ± 10.6 岁,患病率为 12.4% (95% CI, 8.95% to 15.82%),其中女性患病率为 13.6%,男性患病率为 12.4%,但性别无统计学差异($p=0.528$),有 SAH 或 ICA 家族史发病率为 21.6%,无有 SAH 或 ICA 家族史发病率为 11.0%,SAH 或 ICA 家族史不明确者发病率为 8.3%。筛查共发现 54 枚动脉瘤,平均直径 3.85 ± 3.25 mm (1.7 mm 到 25 mm),3 mm 以下 22 枚,3-6 mm 26 枚,6-10 mm 5 枚,大于 10 mm 一枚;其中囊状动脉瘤 53 枚,梭状动脉瘤 1 枚,全部位于前循环(颈内动脉 26 枚,大脑中动脉 14 枚,前交通动脉 1 枚,大脑前动脉 1 枚),后循环未发现动脉瘤(见表 2)。

对是否患 ICA,高血压($P=0.722$)、多囊肝($P=0.517$)、肾功能($P=0.302$)均无明显统计学差异,但高血压持续时间($P=0.001$)有统计学意义。

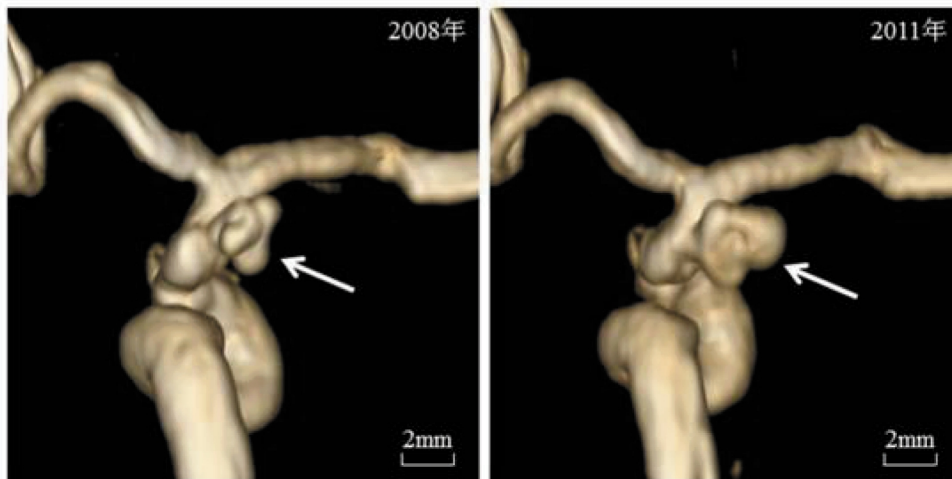


Fig. 1 Male, 59 years old, diagnosed as ADPKD 11 years ago; followed-up for 42 months, the ICA which located in right internal carotid artery grew from 3.1mm to 4.2mm

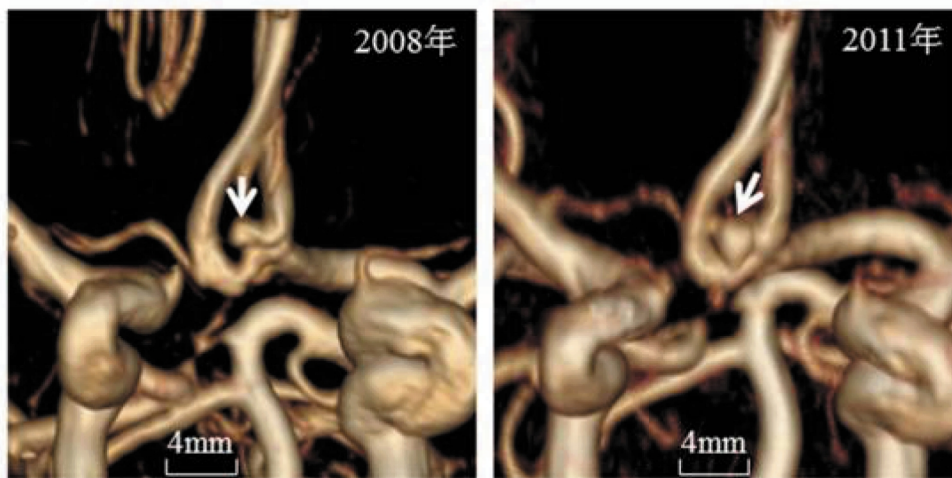


Fig.2 Female, 52 years old, diagnosed as ADPKD 9 years ago; followed-up for 45 months, the ICA which located in Anterior communicating artery grew from 2.1mm to 3.6mm

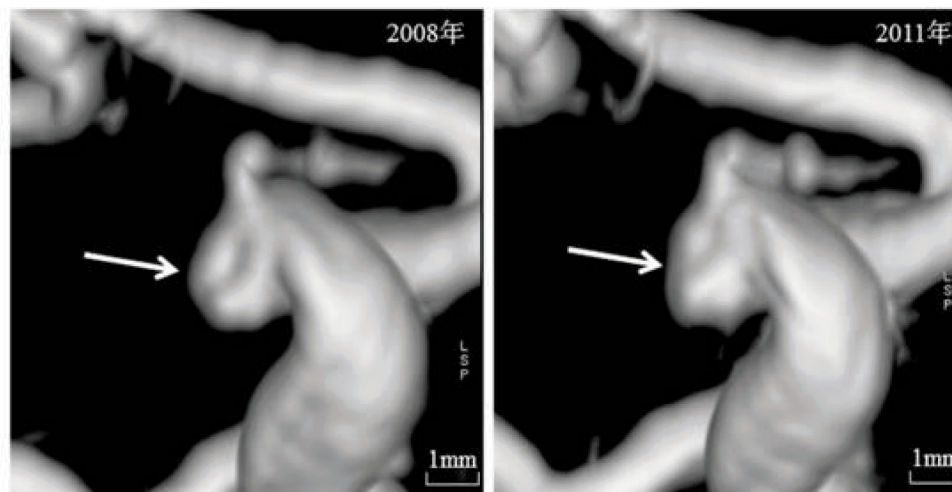


Fig.3 Female, 59 years old, diagnosed as ADPKD 13 years ago; followed-up for 40 months, the ICA size were 2.3 mm and 2.4 mm, respectively

2.2 MRI 的复查结果

对筛查发现有 ICA 的 44 位患者,于 2011 年 11 月 -2012 年 1 月复查头部 MRI,其中有 23 位患者失访,其余 21 名患者 (27 枚动脉瘤)随访,平均随访 43.5 ± 4.3 月。复查发现两位患者颅内动脉瘤增大,一例患者从 3.1 mm 增至 4.2 mm (图 1),另一例从 2.1 mm 增至 3.6 mm (图 2),扩大率为 7.4%;未发现新生 I-

CA;其余 25 枚动脉瘤大小无明显变化;未发现新生动脉瘤。27 枚动脉瘤平均直径 3.50 ± 2.36 mm (1.4 mm-6.3 mm)。图 3 为动脉瘤大小无明显变化患者头部 MRI 结果。

2.3 临床随访结果

除 23 例患者失访外,其余 21 例患者平均随访 43.5 ± 4.3 月,无患者死亡或颅内动脉瘤破裂,其中 3 例患者接受外科手

表 2 54 枚动脉瘤的特征

Table 2 Characteristics of 54 cases of ICAs

ICA Detected by MR Angiography	No.
Types of ICAs	
Saccular ICA	53
Fusiform ICA	1
Location of aneurysms	
Internal carotid artery	26
Middle cerebral artery	14
Anterior communicating artery	12
Anterior cerebral artery	1
Posterior circulation	0
Patients with multiple aneurysms	
Patients with 2 aneurysms	6
Patients with 3 aneurysms	2

术治疗,1例失败。7例肾功能正常,5例从正常发展到轻度异常,10位肾功能异常患者肾功能不同程度恶化,其中7例发张为终末期肾病,4位患者并接受肾脏替代治疗;无新增蛋白尿患者,其中10例蛋白尿阴性,3例($\bar{x} \pm s$),9例蛋白尿阳性;5例电解质检查 Ca^{2+} 、 P^{3+} 代谢紊乱,且都是终末期肾病患者。21位患者有13例合并多囊肝,所有患者肝功能正常。

3 讨论

ADPKD患者并发颅内动脉瘤首先由大样本尸检发现,近年来多由影像学检查证实^[34]。虽然,ADPKD患者发生颅内动脉瘤的概率较高,但确切的发病率并不清楚,ADPKD患者颅内动脉瘤的特征知之甚少。本研究发现ADPKD并发颅内动脉瘤的发病率是12.4%,比Huston and Ruggieri (分别为10%和11.7%)报道的高^[56]。另外,颅内动脉瘤的发病率和是否有脑卒中家族史密切相关,和无明确脑卒中家族史相比RR:1.968(95%可信区间,1.57-2.67)。所以,是否有脑卒中家族史是ADPKD筛查颅内动脉瘤的指针。ADPKD患者并发颅内动脉瘤的概率约8%,是正常人群5倍;我们的研究数据是患病率为12.4%(95%CI, 8.95% to 15.82%);另外,有SAH或ICA家族史发病率为16%,无有SAH或ICA家族史发病率为6.0%^[1];我们的研究数据是有SAH或ICA家族史发病率为21.6%,无有SAH或ICA家族史发病率为11.0%,SAH或ICA家族史不明确者发病率为8.3%。

本研究和先前文献报道不相同的方面还包括:(1)文献报道颅内动脉瘤最常见的部位是大脑中动脉,而我们的研究显示为颈内动脉;(2)既往文献报道,颅内动脉瘤有5-10%发生于后循环,我们在后循环并未发现颅内动脉瘤;(3)ADPKD患者发生大动脉瘤(大于10mm)的概率较高,高达27%,我们并未发现大动脉瘤,认为这些差异可能于研究对象的种族有关。

动脉瘤大小是动脉瘤扩大独立危险因素,直径<5mm扩大的风险较低。荷兰一项针对93位患者,125枚动脉瘤的研究,平均年龄51岁,随访15个月,发现3.2%有轻度扩大(0.5-1.5mm)^[7]。J.H III等报道165位患者,191枚动脉瘤,平均

年龄64岁,随访47月,<8mm、8-12mm、>12mm,动脉瘤扩大概率分别为6.9%、25%、83%^[8]。Maria V等长达10年针对ADPKD合并颅内动脉瘤,45枚动脉瘤随访研究,发现新增动脉瘤1枚,2枚动脉瘤有轻度增大,增大率为6.6%^[9]。本研究发现动脉瘤扩大率为7.4%,结果表明,合并ADPKD的ICA患者较一般ICA患者扩大的风险并未增加。

本研究中,<50岁患者中动脉瘤无扩大,表明无症状小动脉瘤患者中,年轻患者的动脉瘤生长风险很低,和Maria V等的研究结果相符。既往有一些针对无ADPKD颅内动脉瘤人群的研究,但一般针对老年人群,且多合并SAH家族史或(和)有神经症状,和本研究比较价值不大。两个日本的研究,分别针对140和130病例平均随访17.7月和29.3月,平均年龄为62.8和68.8岁,发现年生长率为6.4%和10.8%^[10,11]。Mike Clarke在5个纵向和15个病例对照研究的meta分析中,吸烟与蛛网膜下腔出血关系密切。在人群中现在吸烟和从不吸烟的,风险比值是2.2(95%CI 1.3-3.6)。另外,有证据表明吸烟加速动脉瘤的生长,但机制不明确,有研究者发现吸烟增加弹性蛋白酶的活性和\或降低了 $\alpha 1$ -抗胰蛋白酶活性,导致“弹性蛋白酶\ $\alpha 1$ -抗胰蛋白酶”比值变化而促进动脉瘤的形成生长和出血。

颅内动脉瘤破裂的危险因素仍存在争议。Wiebers等研究发现,排除既往SAH动脉瘤患者,其余所有患者破裂率1.4%/年,但是直径<10mm动脉瘤无破裂^[12]。接着日本和芬兰的神经外科医生报道,动脉瘤破裂率在1.3-2.3%/年,且危险性和动脉瘤的大小相关,动脉瘤越大,破裂的危险性增加,和Wiebers等报道不同的是,小动脉瘤,甚至直径<5mm动脉瘤也可能破裂^[13-16]。未破裂颅内动脉瘤国际研究(ISUIA)是针对颅内动脉瘤破裂危险因素最大的研究,ISUIA 1回顾性研究12023患者/年,约50%有SAH病史,所有患者的年破裂率为0.3%,直径10mm以上患者,既往有SAH病史年破裂率为0.5%,而无SAH病史的破裂率仅为0.05%^[17]。ISUIA II非随机前瞻性研究6544患者/年,无SAH病史患者动脉瘤大小<7、7-12、13-24、 ≥ 25 mm,5年累计破裂率在前循环(颈内动脉、前交通动脉、大脑前动脉、大脑中动脉)分别为0%、2.6%、14.5%和40%,在后循环5年累

计破裂率分别为2.5%、14.5%、18.4%和50%^[18]。Maria V等非随机前瞻性研究ADPKD合并ICA患者316患者-年,大部分动脉瘤<7 mm,无动脉瘤破裂。我们的研究仅96.3患者-年,在规模上远远少于上面所列的研究,所有动脉瘤直径少于7 mm,且都位于前循环,发现无动脉瘤的破裂,表明ADPKD合并ICA患者较一般人群破裂的危险性并未增加,和Maria V等的研究相符。

动脉瘤破裂的其他危险因素包括SAH家族史、吸烟和高血压^[19]。瑞典住院病例登记研究,有一个亲戚或2个和以上亲戚患SAH是无SAH家族史患者发生SAH的2.15倍和50倍^[20]。家族性颅内动脉瘤研究发现,在动脉瘤大小和位置相似的情况下,有两兄妹或3个以上亲戚有动脉瘤或SAH,同时吸烟和高血压,动脉瘤年破裂率为1.2%,是ISUIA研究人群的17倍^[21]。我们的研究:30%患者有SAH家族史,患高血压94.6%,并无动脉瘤破裂,和Maria V等的研究相符,提示ADPKD合并ICA较一般人群动脉瘤破裂的危险性并未显著提高。但我们要重视这些危险因素,这对ADPKD患者动脉瘤的管理相当重要。

总之,ADPKD患者行头部MRI筛查颅内动脉瘤非常必要,尤其是年龄≥30岁和有脑卒中家族史的患者,绝大部分ADPKD患者合并的颅内动脉瘤直径较小且都位于前循环,大多数患者的颅内动脉瘤无明显增大,也无破裂,但建议对于此类患者的颅内动脉瘤可延长随访问隔时间。

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