Title page

Title

Autosomal dominant polycystic kidney disease and coronary artery dissection or aneurysm: a systematic review

Authors

Joana Briosa Neves[a], MD; Filipe Brogueira Rodrigues[a,b], MD; José António Lopes[c], MD PhD

Affiliations

[a] Department of Medicine, Centro Hospitalar Lisboa Norte, Lisbon, Portugal

[b] Laboratory of Clinical Pharmacology and Therapeutics, Faculty of Medicine, University of Lisbon, Portugal and

Clinical Pharmacology Unit, Instituto de Medicina Molecular, Lisbon, Portugal

[c] Department of Nephrology and Renal Transplantation, Centro Hospitalar Lisboa Norte, Lisbon, Portugal

Corresponding author

José António Lopes, MD, PhD

Department of Nephrology and Renal Transplantation, Centro Hospitalar Lisboa Norte, Hospital de Santa Maria

Av. Prof. Egas Moniz

1649-035 Lisboa

Portugal

Telephone: +351961203912

Fax: +351217805679

E-mail: jalopes93@hotmail.com

Contacts of other authors

Joana Briosa Neves, MD

Department of Medicine

Centro Hospitalar Lisboa Norte

Hospital de Santa Maria

Av. Prof. Egas Moniz

1649-035 Lisboa

Portugal

E-mail: jbriosaneves@gmail.com

Filipe Brogueira Rodrigues, MD

Department of Medicine, Centro Hospitalar Lisboa Norte, Hospital de Santa Maria

Laboratory of Clinical Pharmacology and Therapeutics, Faculty of Medicine, University of Lisbon

Clinical Pharmacology Unit, Instituto de Medicina Molecular

Address for all affiliations:

Av. Prof. Egas Moniz

1649-035 Lisboa

Portugal

E-mail: filipebrodrigues@gmail.com

Conflict of Interest Statement

The author has completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. The authors have declared that no conflict of interest exists.

Contributions

JAL is the guarantor. All authors contributed to study design, development of selection criteria, data extraction criteria, results' interpretation and discussion. JBN and FBR developed the search strategy, conducted the report screening, study inclusion, and data extraction, and wrote the first manuscript draft. JAL solved disagreements between JBN and FBR regarding study inclusion and data extraction. JAL also offered expertise on autosomal dominant polycystic kidney disease. All authors read, provided feedback and approved the final manuscript.

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Autosomal dominant polycystic kidney disease and coronary artery dissection or aneurysm: a systematic review

Abstract

Importance: Autosomal dominant polycystic kidney disease (ADPKD) has been associated with cardiovascular abnormalities such as intracranial and aortic aneuryms.

Objective: To systematically reviewed case reports and case series of ADPKD patients with coronary artery dissection or aneurysm.

Evidence Review: Systematic review registration number: CRD42015015723. Data sources: MEDLINE, Web of Science and OpenGrey. Reference lists of studies. Study selection: Published case reports and case series. Data extraction: Two parties analyzed the studies. Disagreements were solved by consensus or by a third party. Funding: None

Findings: The reports of 23 patients (22 from 17 studies – 6 with coronary artery dissection and 16 with coronary artery aneurysm – and 1 with coronary dissection here reported) were analyzed. Most patients were symptomatic. Coronary dissection showed female and left descending anterior artery predominance, features similar to non-ADPKD patients, but a median diagnostic age below expected (41 vs 50 years old). Coronary aneurysms had male and right coronary artery predominance but lower median diagnostic age (44 years old) and higher rate of multiple vessel affection than reported for non-ADPKD patients.

Conclusion and relevance: Clinical disparities may suggest a different mechanism of aneurysm formation comparing to the population without ADPKD. Nevertheless, lack of access to data of one patient and text of one article limited our conclusions. Coronary aneurysms and dissections represent a source of coronary syndromes and death in ADPKD. Mutation of ADPKD-related genes may predispose to coronary abnormalities, especially aneurysms. Further analysis regarding this association is necessary.

Introduction

Autosomal dominant polycystic kidney disease (ADPKD) is the most frequent hereditary renal cystic disease[1]. This monogenic disorder is caused by mutation with loss of function of one of two genes: PKD1, that encodes polycystin-1, and PKD2, that encodes polycystin-2[2]. PKD1 mutation is responsible for 85% of cases, and PKD2 mutation for the remainder[1].

ADPKD is associated with a wide phenotypic range. Manifestations include renal, hepatic, pancreatic, seminal vesicle and arachnoid cysts, intracranial and aortic aneurysms, cardiac valvular abnormalities, colonic diverticula, and bronchiectasis[3]. Although apparently rare, arterial aneurysms and dissections on other locations, such as the coronary arteries, have also been described[3].

In this article we conduct a systematic review of case reports and series of ADPKD patients who developed coronary artery dissection or aneurysm and include the case of a patient followed in our centre.

2. Materials and Methods

2.1. Case report

The case report was prepared after patient consent as defined by the ethical guidelines at Centro Hospitalar Lisboa Norte, Portugal. Data was gathered retrospectively from medical records. For the purposes of case reporting we used STROBE[4] and CARE guidelines[5].

2.2. Systematic review

The systematic review was conducted in line with MOOSE[6] and PRISMA[7] statements. The study protocol was published at PROSPERO (CRD42015015723; available at: http://www.crd.york.ac.uk/PROSPERO_REBRANDING/display_ record.asp?ID=CRD42015015723).

2.2.1. Eligibility criteria

All case reports and case series reporting original cases of pediatric and adult ADPKD patients with coronary artery dissection or aneurysm were accepted. Only published data was accepted. Other types of studies, and abstracts oral or poster presentations were excluded. There were no language or time restrictions and non-English reports were translated.

2.2.2. Definitions

In at-risk individuals, ADPKD diagnosis was based on the presence of: at least three renal cysts unilaterally or bilaterally in individuals between 15 and 39 years old; at least two cysts in each kidney in individuals between 40 and 59 years old; and of four or more cysts in each kidney in individuals over 60 years old[8].

Coronary artery dissection was defined as: contrast dye staining of arterial wall with multiple radiolucent lumen; or appreciable (often subtle) abrupt change in arterial caliber, with demarcation from normal diameter to diffuse narrowing; or long (11–20 mm), hazy or linear stenosis without evidence of atherosclerotic changes in other coronary arteries[9].

The definition of coronary artery aneurysm or ectasia used was: focal or segmental dilation that exceeds by 50% the diameter of healthy adjacent reference segments or vessels[10]. Focal or segmental dilations of inferior diameter, sometimes mentioned as "minor ectasias", were not considered for analysis.

2.2.3. Data sources

Electronic database identification of reports was conducted on MEDLINE and Web of Science. Grey literature was searched via appropriate databases (i.e.: OpenGrey). The last search was done on 27 December 2014. Whenever needed authors were contacted via email for further access to data. References of included studies were crosschecked.

2.2.4. Search strategy

The developed search strategy for all databases combined the terms (Autosomal Dominant Polycystic Kidney Disease) with (Coronary Artery Diseases OR Coronary Aneurysm OR Coronary Dissection). A highly sensitive filter was used to avoid retrieval of non-observational studies[11]. Participants were restricted to humans. All terms were searched as free-text and controlled vocabulary. The reference lists of selected studies were crosschecked for additional potentially eligible studies and cited reference research was done using studies' titles and authors.

2.2.5. Study selection

Reports retrieved through electronic identification were screened for eligibility by title and abstract analysis. Exclusion reasons were not recorded. The full text of potentially eligible studies was screened for appropriateness for inclusion. Exclusion reasons were recorded. Two screeners (FBR, JBN) conducted this process. Disagreements were solved by consensus or by a third party (JAL). The Cohen's kappa (κ) coefficient was used to calculate inter-observer bias[12].

2.2.6. Data extraction

Two independent parties (FBR, JBN) extracted data from the included studies' full text to an electronic form. Disagreements were solved by consensus or by a third party (JAL).

2.2.7. Data synthesis and analysis

The following data were extracted: surname of first author, publication year, clinical characteristics, presence and family history of extra-renal ADPKD manifestations, diagnosis of coronary dissection or aneurysm, local treatment, and outcome. Gathered data were subject to descriptive analysis.

3. Results

3.1. Case report

We report the case of a female Portuguese patient, with 41 years old, and a diagnosis of ADPKD with renal and hepatic cysts, without mutation analysis. Currently overweight (body mass index 28 kg/m^2), the patient had normal renal function and no other cardiovascular risk factors, namely arterial hypertension. Her family history was remarkable for ADPKD: her father and brother had renal cysts but no extra-renal manifestations.

The patient was asymptomatic until 1 week before admission, when she started complaining of progressively worsening precordial discomfort with irradiation to both upper limbs. She went to see her family physician, where an electrocardiogram (EKG) was ordered. An elevation of the ST segment on DIII and aVF leads prompted the diagnosis of inferior myocardial infarction. The patient was then transferred to a central hospital, where an urgent coronary catheterization showed a co-dominant system, with 99% stenosis of the circumflex artery suggestive of either diffuse or spastic disease and 30% ostial stenosis of the right coronary artery. Balloon angioplasty was performed on the circumflex artery, with an end-thrombolysis in myocardial infarction (TIMI) flow grade of 3.

The patient remained asymptomatic for 6 days, after which anterior thoracic discomfort recurred. The EKG remained unchanged but troponin I levels raised from normal values to 2.45ng/ml (laboratory cut-off: 0.02ng/ml). A second coronary catheterization was performed, revealing a permeable circumflex artery despite complete right coronary artery occlusion due to dissection (Figure 1a). Reperfusion was accomplished after proximal placement of a drug-eluting stent under optical coherence tomography (OCT) guidance, with an end-TIMI flow grade of 3 (Figure 1b). Thereafter the patient became asymptomatic and troponin I levels progressively normalized.

At two months of follow-up, coronary catheterization demonstrated maintenance of dissection of the right coronary artery (Figure 2a). Two drug-eluting stents were placed distally to the first under OCT guidance with an end-TIMI flow grade of 3, except for the distal part of the vessel, which was very thin and remained dissected (Figure 2b). At six months of follow-up, the patient remained asymptomatic.

3.2. Systematic review

3.2.1. Study selection

Database and manual search yielded 113 records. After deduplication, 103 records were screened and 84 were discarded after title and abstract inspection due to lack of eligibility. A κ of 0.70 (95%CI 0.50-0.90) was calculated for inter-observer bias, reflecting good agreement between screeners[12]. Of the 19 potentially eligible studies, the full text was unavailable for 1, even after contacting the first author and the journal editor. The full text of 18 potentially eligible studies was analyzed: 1 was excluded due to lack of eligibility criteria and 17 were included for analysis[13-29] (Figure 3).

3.2.2. Study characteristics

All included studies were case reports except for three cases series[15-17]. All were in English but one published in Portuguese[25]. Publication years ranged from 1993 to 2014. The studies had widespread distribution: 6 in Europe (Sweden, Germany, The Netherlands, Switzerland, France, and Italy), 6 in Asia (Israel, China, Iran, Japan, Turkey, and Korea), 3 in America (USA, and Brazil) and 2 in Oceania (Australia).

3.3. Analysis of study participants characteristics

The included studies reported on 23 patients but one had insufficient data regarding one patient[16]. After unsuccessful author contact, the latter patient was excluded from analysis.

Patient data extracted from the selected studies and from the case reported in this article are summarized on tables 1 and 2, representing a total of 23 patients: 7 (30.4%) with coronary artery dissection and 16 (69.6%) with coronary artery aneurysm. Genetic status was unknown for all patients.

3.3.1. Manifestations, diagnosis, and treatment of ADPKD patients with coronary artery dissection

Most patients were female (n=5; 71.4%). The median age of diagnosis was 41 years (range: 36-59). Extra-renal manifestations of ADPKD were reported as follows: two patients had hepatic cysts (patients 1, and 6), one had cardiac valvulopathies (patient 2 had mitral valve prolapse and regurgitation, and tricuspid valve prolapse), and none had extra-coronary aneurysms or dissections.

End-stage renal disease (ESRD) was absent in all coronary dissection patients. Arterial hypertension was diagnosed in two patients (28.6%) and coronary atherosclerosis was described in another two patients, one of them on the same dissected artery (left anterior descending artery on patient 5). None of the cases reported association with connective tissue disorders, systemic inflammatory diseases, or the peripartum period. In one (patient 2) the use of combined hormone therapy was registered.

None of the patients had a positive family history of coronary or extra-coronary aneurysms or dissections.

All cases were symptomatic: two patients (28.6%) had angina and five (71.4%) had a myocardial infarction. The primary method of diagnosis was coronary angiography (n=7, 100%). In one case (14.3%), computer tomography coronary angiography was also diagnostic. The most frequently affected artery was the left anterior descending vessel (n=5; 71.4%).

Coronary angioplasty was conducted on 4 patients (57.1%), with good control of symptoms in 3 patients. Outcome was not reported in all patients with conservative management and in one who underwent angioplasty.

3.3.2. Manifestations, diagnosis, and treatment of ADPKD patients with coronary artery aneurysm

Male predominance was registered in coronary aneurysm patients (n=10; 76.9% of all patients with known gender). The median age of diagnosis was 44 years (range: 23-78). Extra-renal manifestations of ADPKD were reported as follows: four patients had hepatic cysts (patients 8, 20, 22, and 23); five had cardiac valvulopathies (patients 8, and 23 had mitral valve prolapse; patients 17, 22, and 23 had mitral regurgitation; and patients 18, and 22

had aortic regurgitation); and four had extra-coronary aneurysms (patients 18, 21, and 23 had aortic aneurysms; patient 20 had aneurysms on one renal artery; patient 23 had bilateral femoral artery aneurysms; and patient 18 had bilateral iliac artery aneurysms).

Six patients had ESRD (patients 8, 17, and 18 were transplant recipients, and patients 9, 20, and 23 were on hemodialysis). Arterial hypertension was diagnosed in five patients with coronary aneurysm (50% of all patients with reported blood pressure status). Six patients with coronary aneurysms had atherosclerosis, two of them on the same aneurysmatic artery (right coronary artery on patient 8 and right and left coronary arteries on patient 23). None of the cases reported association with connective tissue disorders, systemic inflammatory diseases, hormonal therapy, or the peripartum period.

A positive family history of coronary aneurysms was registered for patients 13, 14, 15, and 16. No family history of other aneurysmatic or dissecting complications was reported.

Six patients (46.1%) were asymptomatic. However four cases (30.8%) presented with myocardial infarction and three (23.1%) with angina. In 13 cases (81.3%), coronary aneurysms were diagnosed by coronary angiography. Three cases were diagnosed by other methods: one (6.3%) during autopsy, one (6.3%) with computer tomography coronary angiography, and one (6.3%) with transthoracic echocardiography.

In six cases (40%) multiple coronary arteries were aneurysmatic, with three-vessel aneurysms in three patients (20%). Overall, the right coronary was the most affected vessel (n=7), followed by the left anterior descending (n=6), and the circumflex artery (n=6).

Local treatment was reported in a single patient (patient 11): a coronary bypass surgery that, due to operative complications, lead to patient death. Two other patients died, one due to sepsis (patient 18) and another due to rupture of the coronary aneurysm (patient 21). Regarding the remaining patients, only two reported outcomes and both remained asymptomatic at follow-up (patients 22 and 23).

4. **Discussion**

In this study we report and systematically analyze previous reports of coronary dissection and aneurysm in ADPKD patients.

Cardiovascular disease is the main cause of death among ADPKD patients, with half of the mortality cases being attributable to ischemic heart disease[30]. Ischemic heart disease is highly prevalent in ADPKD and is present even before ESRD[31]. However, coronary atherosclerosis may not be the sole source of cardiac associated-morbidity and mortality in ADPKD. As the present study shows, coronary artery dissections and aneurysms also represent a cause of angina, myocardial infarction, and death in ADPKD patients.

Polycystin-1 and -2, the two mutated proteins responsible for ADPKD[2], are expressed in smooth muscle cells and myofibroblasts of the tunica media and in the endothelial layer of vessels[32]. It has been proposed that mutation of either of these proteins could contribute to vascular wall weakness[32]. An autopsy analysis revealed focal media defects on extracranial arteries that could represent precursor lesions of aneurysms[24]. Thus, mutation of ADPKD-related genes could be responsible for an arteriopathy that predisposes to aneurysm formation or vessel wall dissection.

Concerning the clinical case here reported we must acknowledge that, especially without access to images from the first coronary angiography, it is difficult to classify the right coronary artery dissection culpable for the second coronary syndrome as spontaneous or secondary to endovascular manipulation. Spontaneous coronary artery dissections are rare events. However, in this case balloon angioplasty was only performed on the circumflex artery and the rates of dissection solely due to guide-wire insertion are also low. Even if the dissection was triggered by the angiographic manipulation, we cannot ascertain whether the patient already had vessel weakness – either due to atherosclerosis or due to an arteriopathy caused by mutation of ADPKD genes.

With regards to coronary artery dissection, the findings of the present study are in line with previous reports for non-ADPKD patients, such as female predominance, age of presentation before 50 years old and left anterior descending as the most affected artery[33]. Coronary atherosclerosis and use of hormonal therapy[33] were the only potentially predisposing factors of coronary artery dissection denoted here. Despite previous reports of familial association of aortic dissections on ADPKD individuals[34], we did not observe the same for coronary dissections.

In the majority of the cases described, including the clinical case reported, percutaneous intervention with stent placement was the therapy of choice and provided good symptomatic relief. Nevertheless, half of patients maintained a dissected vessel on follow-up. The overall success rate described for percutaneous intervention in dissection is poor[33] and spontaneous resolution has also been described after dissection[35].

As far as coronary aneurysms in ADPKD patients are concerned, a controlled case series has reported a higher prevalence than in the general population undergoing coronary angiography[16]. In accordance to previous reports[36, 37], we registered male predominance, frequent concomitant presence of atherosclerosis and arterial hypertension and right coronary artery predominance. However, the median age at diagnosis was lower than expected – we observed a median age of diagnosis of 44 years and previous reports on general population note that only 16% of patients are diagnosed before reaching 50 years old[38]. Multiple coronary artery involvement was also more frequent than reported for non-ADPKD patients[36, 37], and high rates of personal and family history of aneurysmatic burden on other extracranial vessels were registered.

Only one ADPKD patient with coronary aneurysm underwent coronary bypass surgery. The largest therapeutic experience with coronary aneurysms is still surgical[36] but recent, minimally-invasive, percutaneous treatments to exclude the aneurysm appear to lead to reduced complication rates[39].

Whilst the clinical characteristics of coronary dissection in ADPKD patients appear to mimic the ones for non-ADPKD individuals, we believe that the younger age at diagnosis, the aneurysmatic involvement of other vessels, the high family burden and the more frequent involvement of multiple arteries suggest a different mechanism of aneurysm formation as compared to the population without ADPKD diagnosis.

The clinical course of coronary aneurysms can be complicated by thrombosis, thromboembolism, formation of arteriovenous fistulae, vasospasm, and rupture[36]. We registered a high rate of myocardial infarction-associated diagnosis, and a complicated aneurysm and an operative complication as causes of death of two of the reported patients. Further studies are needed to confirm if coronary artery aneurysms confer worse outcomes to ADPKD patients and if asymptomatic diagnosis is worthwhile to prevent deleterious events.

Finally, the reported proportions of patients with arterial hypertension and coronary atherosclerosis in this systematic review are lower (<50%) than their incidence in non-ESRD ADPKD patients[40, 41]. This indicates that these may not have been predisposing factors for coronary abnormalities and that other sources of vessel weakness may be at play.

4.1. Study limitations

The limitations of the present analysis are the lack of access to all published cases, the small number of patients, the short-follow up and the incomplete outcome reporting of most studies. However, its systematic nature allows for conclusions of greatly enhanced quality.

5. Conclusions

Mutation of ADPKD-related genes could lead to an arteriopathy that predisposes to coronary artery abnormalities. Atherosclerosis may not be the sole source of cardiac associated-morbidity and mortality in ADPKD since dissections and aneurysms also represent a cause of angina, myocardial infarction, and death in ADPKD patients. This study highlights the need for more extensive analysis to evaluate the prevalence, risk factors and adequate intervention in these individuals – analysis of data from patients included in the CRISP cohort[42] and HALT-PKD trials[43] may help further elucidate on these matters.

6. Acknowledgments

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Legend of figures

Figure 1. Coronary angiography showing a) proximal dissection of the right coronary artery and b) reperfusion after proximal drug-eluting stent placement.

Figure 2. Coronary angiography showing a) middle and distal dissection of the right coronary artery and b) reperfusion after placement of two drug-eluting stents after the previously placed proximal stent.

Figure 3. Study selection flow diagram according to PRISMA 2009