

Hypertensive Encephalopathy and Renal Failure in a Young Man

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• Online Data Supplement

Presentation of Case

A 35-year-old male physician, who worked in a Scottish hospital, became unwell while attending a medical conference in the north of England. His colleagues and family became concerned when they were unable to establish contact with him, prompting a search of the conference facilities. He was found drowsy and confused in his hotel bedroom. This presentation was preceded by 7 weeks of blurred vision and headaches. An arthroscopy had been cancelled 15 years previously because of high blood pressure. The patient was under the impression his blood pressure had normalized over subsequent months but this was not documented. There was no significant family history. He was on no regular medication, was a nonsmoker, and took only occasional alcohol.

The patient weighed 180 kg. His blood pressure (BP) in the emergency department was 250/180 mm Hg. He had bilateral posterior shoulder dislocations and had bitten his tongue extensively. He went on to have uncontrolled seizures necessitating intubation and ventilation. After stabilization, fundoscopy revealed bilateral flame hemorrhages and papilledema.

He had a stormy course on the Intensive Care unit with recurrent seizures and a failed attempt at extubation. When extubated for the second time, he was immobile because of the shoulder dislocations, cortically blind, and had extensive retrograde amnesia. His BP was initially controlled with intravenous labetalol.

Initial investigations revealed significant renal impairment (Table). Urinalysis disclosed blood (++++) and protein (++++). There was no evidence of hemolysis on a blood film.

C-reactive protein was elevated, and serum albumin was low, compatible with an inflammatory response.

Discussion: Further Investigation

Dhaun: Would you like any further information? What further investigations would you want at this stage if you were looking after this man?

Dominiczak: We need to see the kidneys. An ultrasound would be good.

Dhaun: Would anybody request a computed tomographic scan of the head?

Audience: [Generalized nodding.] Urine.

Dhaun: Would you like some more quantification in the urine or analysis of the urine?

Audience: Proteinuria

Alwakeel: Did you examine the fundus? Fundus examination and listening for arterial bruits (over the renal, carotid and femoral arteries) is important, particularly in a patient with hypertension at such a young age.

Dhaun: We did do the fundoscopy and there were flame hemorrhages and papilledema.

Staessen: I think in this patient I would do brain imaging and I would do lumbar puncture for cerebrospinal fluid to see if there is any blood in it.

Gikonyo: Urine toxicology. I had a patient like this recently who happened to have misused cocaine.

Jennings: And while we are collecting urine, metanephrines, or some sort of catecholamine screening for pheochromocytoma.

The opinions expressed in this article are not necessarily those of the editors or of the American Heart Association.

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Further Investigation and Initial Diagnosis

Thank you for your suggestions; we did a number of these tests. His ECG did not show left ventricular hypertrophy by voltage criteria, but he did have concentric left ventricular hypertrophy on echocardiogram. He had both computed tomographic and magnetic resonance imaging brain scans. These revealed hyperintense, white matter signal in the occipital and parietal lobes bilaterally, more evident on the right side (Figure 1A).

In the clinical context, we felt this was compatible with posterior reversible encephalopathy syndrome, which may be caused by accelerated hypertension (or fluctuations in BP), renal failure, immunosuppressive therapy, or autoimmune conditions.¹ The neuroradiologist offered a differential diagnosis that included stroke and demyelination.

The renal ultrasound scan showed 2 unusually large kidneys, measuring 18 and 16 cm (In a man of this size, a normal bipolar length would be \approx 12 cm). Both contained multiple cysts with the largest of these measuring 6 cm, on the right side.

Additional laboratory tests were performed (Table). Random plasma cortisol was elevated as was 24-hour urinary cortisol excretion. Plasma and urine catecholamines were within the reference range. Additional immunologic tests and cerebrospinal fluid analysis were normal (Table). He had proteinuria (urinary protein:creatinine ratio of 487 mg/g). The serum creatinine was elevated, in keeping with his seizures. Cholesterol was 3.9 mmol/L, and the parathyroid hormone of 10.6 pmol/L was above the reference range, in keeping with an element of chronic kidney disease (CKD).

In light of the neuroimaging, a thrombophilia screen was performed. This demonstrated a mutation in the prothrombin gene (PT20210A heterozygote), which confers an increased risk of venous thrombosis and also of premature atherosclerosis.² We remind you that the patient and his family had no history of venous thrombosis.

Discussion: Renal Diagnosis

Dhaun: This gentleman was referred to our nephrology service. We felt the likely diagnosis was autosomal dominant

Table. Laboratory Investigations

Tests	Results	Reference Ranges
Results of initial blood tests		
BUN, mg/dL	53.8*	(7.0–18.5)
Creatinine, mg/dL	4.02*	(0.67–1.36)
Sodium, mmol/L	140	(135–145)
Potassium, mmol/L	3.7	(3.6–5.0)
Bilirubin, μ mol/L	19	(3–21)
ALT, U/L	101*	(10–50)
ALP, U/L	104	(40–125)
Albumin, g/L	25*	(30–45)
Calcium, mmol/L	2.07	(2.1–2.6)
Phosphate, mmol/L	1.12	(0.8–1.4)
Hemoglobin, g/dL	13.1*	(13.5–18.0)
WCC, $\times 10^9$ /L	6.9	(4.0–11.0)
Platelets, $\times 10^9$ /L	172	(150–450)
CRP, mg/L	128*	(0–5)
Results of further blood tests		
Cortisol, nmol/L	1284*	...
CK, U/L	16 013*	(55–17)
Cholesterol, mmol/L	3.9	...
PTH, pmol/L	10.6*	(1.6–7.5)
Complement screen (CH50, C3, C4)	normal	
Autoantibody screen (ANA, ENA screen, PR3, MPO, GBM, CCP)	normal/negative	
Cerebrospinal fluid (protein, glucose, bacterial culture, viral PCR)	normal/negative	
Thrombophilia screen	PT20210A heterozygote*	
Results of further urine tests		
Cortisol, nmol/24 h	334*	(20–180)
Metadrenaline, μ mol/24 h	0.3	(0.3–1.7)
Normetadrenaline, μ mol/24 h	2.3	(0.4–3.4)

Reference ranges are shown in brackets. ALT indicates alanine transferase; ALP, alkaline phosphatase; BUN, blood urea nitrogen; CK, creatine kinase; CRP, C-reactive protein; PCR, polymerase chain reaction; PTH, parathyroid hormone; and WCC, white cell count.

*Values outside the reference range.

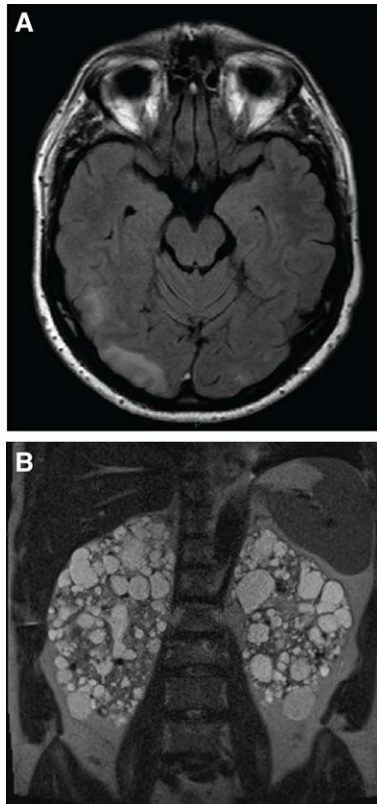


Figure 1. Initial imaging studies. **A**, Magnetic resonance imaging (MRI) brain (T2 flair sequence) demonstrating high signal intensity in the occipital lobes bilaterally (more evident on the right). **B**, MRI abdomen demonstrating numerous cysts in both kidneys.

polycystic kidney disease (ADPKD). Would you like any further information to support or refute this diagnosis?

Abu-Alfa: Why is the proteinuria there? That may be too high a degree of proteinuria for polycystic kidney disease. Could this be acquired cystic disease from longstanding CKD? Why would you obtain cortisol and metanephrines at the time of stress? What would be the value of these tests at that point in time?

Dhaun: In answer to your question about the proteinuria, I agree with you to a degree. ADPKD is a tubular disease, and as such can give rise to tubular proteinuria, typically 0.5 to 1.0 g/d. However, in this setting, the renal hemodynamic effects of uncontrolled hypertension would themselves give rise to a degree of proteinuria. Regarding your question about cortisol, I agree with you that the readings are compatible with stress. Finally, we agree that the textbook list of screening tests for secondary causes of hypertension should be performed and interpreted appropriately.

Dominiczak: Do we know anything more about the family history? ADPKD with this type of advanced kidney disease without any family history would be unusual. “Autosomal dominant” means “autosomal dominant”.

Dhaun: As Professor Dominiczak says, autosomal dominant implies that 50% of the family members should be affected. We will comment on the family history shortly.

Alwakeel: The potassium result is interesting. At presentation, his potassium was 3.7. Usually, when someone has a seizure and has been fitting for some time, the serum potassium is

elevated and the creatine kinase is really high (and also maybe the creatinine) because of myocyte damage. The low potassium in this case could indicate that the patient has malignant hypertension. At the least, other family members should be screened carefully for hypertension.

Dhaun: We will talk about the family history in a minute. As regards potassium and seizures, I agree with you that many things will be abnormal in the biochemical screen around the time of the seizure, such as lactic acid, potassium, and creatine kinase. However, I will remind you that in this case the patient was found at some point after he had been seizing. We don't know how much time had elapsed before he was found. Although I agree with you that potassium may well have been, and probably was, elevated at the time of seizing, maybe the time course was sufficient for him to have cleared any excess serum potassium. The ECG we had from the emergency department was normal and showed no evidence of significant hyperkalemia.

Family History and Further Imaging

We obtained an abdominal computed tomographic and then a magnetic resonance imaging scan (Figure 1B). These showed grossly enlarged kidneys with multiple cysts bilaterally. It also showed a single liver cyst measuring 2.5 cm, but that is not out of keeping with what one might expect in a man of this age.

His family history did not support a diagnosis of ADPKD. Ultrasound screening of his father and sister revealed no renal cysts. Importantly, they were both of an age, where this effectively excluded a diagnosis of ADPKD. His mother died in her 30s of an unrelated cause. It is plausible that she had undiagnosed cystic renal disease.

Autosomal Dominant Polycystic Kidney Disease

So we diagnosed him with ADPKD, one of the commonest monogenic disorders in humans with a prevalence of between 1 in 400 and 1 in 1000. It is caused by mutations in 1 of 2 genes, ADPKD1 or ADPKD2, which encode polycystins 1 and 2, respectively. These are inherited in an autosomal dominant fashion, but $\approx 25\%$ of patients have no prior family history.³ When screening family members, a significant amount of clinically silent disease is detected. Therefore, the true rate of sporadic mutation is thought to be $\approx 5\%$.³ Liver cysts support the diagnosis but are absent in 20% of patients and are more common in women.

There is a differential diagnosis of cystic renal disease, particularly in the absence of a family history.³ Acquired cystic disease is one possibility. However, the cysts were particularly numerous and out of keeping with his degree of renal dysfunction. There are too many cysts throughout both cortex and medulla for it to be simple cystic disease. There were no clinical features of tuberous sclerosis.

Questions From the Audience

Alwakeel: I'm not sure why this patient has this thrombosis. People who have high BP may have propensity for bleeding (internal hemorrhage). But this man has thrombosis. Is there some other reason for thrombosis?

Hunter: I should clarify. We did not demonstrate any thrombus in the patient. We felt his neuroimaging was compatible

with posterior reversible encephalopathy syndrome. However, the differential diagnosis based on the neuroimaging would include thrombosis. Thus, we did a thrombophilia screen and unearthed a thrombotic tendency. Serial imaging demonstrated resolution of these changes, in keeping with posterior reversible encephalopathy syndrome.

Van Den Born: You made a diagnosis of PKD and you had some nice magnetic resonance imaging imaging. Was there any evidence that one of these cysts was compressing the renal artery?

Hunter: That is an excellent question. No there was not any evidence on that imaging.

Progress Over Subsequent Weeks

The patient's serum creatinine fell from 4.02 at presentation, to 1.64 mg/dL over the first week. BP also improved. The patient was transferred to our center. At this point, BP was \approx 160/110 mmHg, and he was prescribed oral doxazosin, amlodipine, and metoprolol, all at maximum therapeutic dose.

Discussion: Next Management Steps

Dhaun: The patient remained hypertensive. His renal function had improved significantly but was still significantly impaired with a creatinine \approx 1.6 mg/dL. Serum creatinine depends not only on glomerular filtration rate but also on age, sex, and muscle mass. His creatinine gave an estimated glomerular filtration rate (Modification of Diet in Renal Disease eGFR) of 35 to 40 mL/min per 1.73 m². However, a 24-hour urine collection estimated a GFR closer to 80 mL/min. Thus, the eGFR was probably underrepresenting his actual GFR. What should we do now?

Alwakeel: We know that angiotensin-converting enzyme (ACE) inhibitors are very good for polycystic kidney disease because they slow the growth of the kidney, and also hypertension is driven by the renin-angiotensin system. I think this should be used in the treatment of the patient's ADPKD. The only thing is this patient has acute kidney injury. With acute kidney injury, one does not like to use ACE inhibition because it may impair renal function. I think doxazosin is not a good drug and it could be replaced with another drug, and when the case is stable, I would put him on an ACE inhibitor.

Audience: I think you must absolutely add the ACE inhibitor or angiotensin receptor blocker (ARB). Did he have sequential measures of proteinuria?

Dhaun: Yes, he did and all proteinuria measurements were below 0.5 g/d (whether measured in a 24-hour collection or extrapolated from albumin:creatinine or protein:creatinine ratios on spot samples). I do take your point about an ACE inhibitor conferring greater renal protection when there is proteinuria. However, the existing data support renin-angiotensin blockade when proteinuria exceeds 0.5 to 1 g/d. The guidelines in the UK suggest that ACE inhibitors or ARBs are prescribed if proteinuria is $>$ 0.5 g/d.⁴

Dominiczak: The opinion here seems to be ACE inhibitor.

Touyz: What is his cerebral status at this point?

Dhaun: He was frustrated at this point. He had been in hospital for 3 to 4 weeks, and his cortical blindness improved gradually. He was immobile in the upper half of his body because of the bilateral shoulder dislocations. His cerebral function had improved over days. He was cognizant and able

to communicate. Although we never assessed it formally, he was probably depressed, which was appropriate for the clinical setting. However, he was able to engage in all treatment discussions.

Abu-Alfa: To follow-up on the acute kidney injury. You must have thought that this was not an acute kidney injury by the time you obtained the 24-hour collection, as he was now in a steady state. If you are comfortable with a GFR of 80 and that he had reached a steady state now, then one can go with an ACE inhibitor. Maybe captopril as a short acting agent in this situation to test how he would react. But if he is not in steady state, then I agree with Dr Alwakeel that one should wait.

Dhaun: I would agree that the GFR is good. It remains unclear whether the elevated serum creatinine of 1.64 mg/dL represents acute kidney injury or CKD. We don't know his historic blood results. However, the elevated parathyroid hormone would support CKD.

Introduction of ACE Inhibitor

An ACE inhibitor (ramipril, 1.25 mg/d) was started. The dose was titrated to 10 mg/d within 48 hours. The patient's serum creatinine rose in response to this. The patient was discharged from hospital at this point. At clinic the following week, BP had improved to 130/85 mmHg. However, creatinine had risen further (from the nadir of 1.64) to 2.79 mg/dL, which is about 70% from baseline. Clinical practice guidelines suggest that if you have a rise in creatinine of $>$ 30%, consideration should be given to withdrawing the ACE inhibitor.⁵

In light of deteriorating renal function, ramipril was stopped. Creatinine fell back to its previous value. This would be in keeping with resolving acute tubular injury, which had been exacerbated by ACE inhibition.

The patient was now at home and taking home BP readings. These were typically 150/100 mmHg with no nocturnal dip. The optimal antihypertensive strategy remained unclear.

Antihypertensive Strategy in ADPKD

Hypertension is common in CKD. Large-scale studies estimate a prevalence of \approx 85% compared with \approx 30% in a matched general population.⁶ It is perhaps more common in ADPKD than it is in CKD of alternative etiologies.^{7,8} It occurs early in the disease, so in patients who have relatively normal renal function with a creatinine clearance of $>$ 90 mL/min, a third of those at a young age will have hypertension. The pathogenesis is thought to rely on activation of the renin-angiotensin system. There are some basic science and human data that support this.^{7,8} In nephrectomy specimens, there is evidence that large cysts compress the renal arteries leading to glomerular ischemia and renin release from juxtaglomerular apparatus. The cyst epithelium, which is derived from the renal tubular epithelium and contains all the molecular machinery required to synthesize renin, is thought to contribute to systemic and intrarenal renin production. Angiotensin II causes hypertension and also drives progression of renal disease by stimulating cyst proliferation and renal fibrosis (Figure 2).

Patients with ADPKD display evidence of plasma volume expansion, elevated plasma renin activity compared with matched controls, and an exaggerated vascular response to ACE inhibition.^{7,8} Historically, renin-angiotensin system

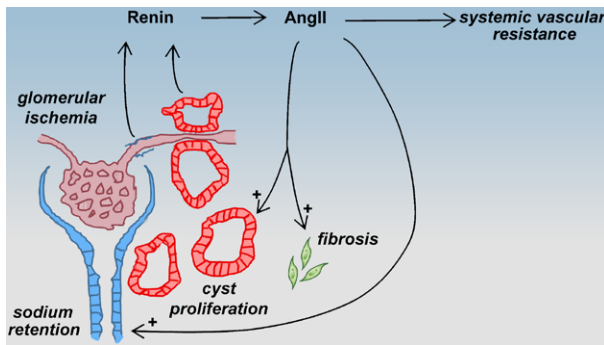


Figure 2. Model for pathogenesis of hypertension and progressive renal failure in autosomal dominant polycystic kidney disease. Large cysts compress the renal arteries leading to glomerular ischemia and renin release from juxtaglomerular apparatus. The cyst epithelium, which is derived from the renal tubular epithelium, contains all the molecular machinery required to synthesize renin, and there is evidence that it contributes to systemic and intrarenal renin production. Angiotensin II (Ang II) causes hypertension and drives progression of renal disease by stimulating cyst proliferation and renal fibrosis.^{7,8}

blockade has been the preferred antihypertensive strategy of choice in ADPKD. However, this has never been directly tested in a randomized control trial (RCT). In a meta-analysis of studies in nondiabetic kidney disease, subgroup analysis in ADPKD patients found that ACE inhibitors had a greater effect on proteinuria than alternative agents, but they had no clear effect on disease progression.⁹ The mean baseline creatinine of 3 mg/dL indicates that these studies were performed in fairly advanced disease.

In 2014, the Halt Progression of Polycystic Kidney Disease (HALT-PKD) trial reported. This large multicenter RCT was designed to test renin-angiotensin blockade in ADPKD patients¹⁰⁻¹² (Note that these data were not available to us at the time, we were making management decisions for the patient discussed here). The trial comprised 2 separate studies, 1 looking at early disease in patients who had an eGFR >60 mL/min and 1 looking at more advanced disease with GFR 25 to 60 mL/min. The studies were designed in this way because the primary outcome was different for each. The early disease study had total kidney volume and the rate of change in kidney volume as the primary outcome, as there are good biomarkers of disease progression. The more advanced disease study had a clinical outcome: a composite of time to death, time to end-stage renal failure, and time to 50% decline of GFR. It was considered unethical to include a group that did not receive any form of renin-angiotensin blockade, so the comparison was made between double blockade (lisinopril and telmisartan) and lisinopril alone. There was no additional benefit of dual blockade over lisinopril alone in either study.

The early disease study also included randomization to target BP of 130/80 mmHg versus 110/75 mmHg. These young patients tended to tolerate that and there was a small benefit in the primary outcome: kidney enlargement was slower in the intensive control group. Taken together, despite reasonably strong evidence from basic science and non-RCT clinical studies, there is actually no RCT evidence that directly supports the use of ACE inhibitors in patients with ADPKD.

Discussion: Antihypertensive Strategy

Dhaun: The patient remained hypertensive. He had stable chronic renal impairment with a creatinine \approx 1.6 mg/dL. His systolic BP was 150 to 160 and diastolic BP >100 mmHg. The options are to add a diuretic, reintroduce ramipril or another agent, or you could do more investigations.

Yazbek: Would you consider using aliskiren in this patient?

Dhaun: Aliskiren is only available on a named patient basis in Scotland. Although it controls BP well, data on longer-term morbidity and mortality (particularly relating to CKD) are lacking. These data are present for the cheaper and effective alternatives of ACE inhibitors or ARBs.

Staessen: What about replacing doxazosin and metoprolol with labetalol which is a combined β - and α -blocker? You don't have to adjust the dose for consideration of renal function and then adding a long-acting, low-dose ARB.

Wang: In your ambulatory BP monitoring, it clearly shows that night time BP even higher, especially systolic, than daytime BP. This means that the patient probably had volume expansion and you used doxazosin at this dosage. Doxazosin may have the problem of volume expansion or retention, so I would suggest that you reintroduce ramipril or other ACE inhibitor with a little lower dosage compared with the previous 10 mg ramipril. The other thing is you should probably also provide a diuretic in the daytime to have a volume decrease. Then you probably would expect better BP control in the evening and overnight.

Therapy Adjustment

Reintroduction of an ACE inhibitor was avoided. Instead, the patient was started on bendroflumethiazide and moxonidine, and his BP did not really change. The patient remains hypertensive, despite having been on multiple antihypertensive agents for 3 months. He played an active role in choosing his therapy. He is a doctor and was back at work now with a busy clinical job. He had been resistant to diuretic therapy, partly through a desire to avoid postural symptoms, and because he was not in a job that would allow him to visit the toilet regularly. This also influenced the timing of his medications. BP is still 170/100 mmHg on home BP readings.

Vlahakos: I realize this person has a high BP that cannot be explained alone by ADPKD. Also, he has a renin effect because you tried twice and creatinine went up and down, and when you gave a diuretic, the pressure was worse. So, try to see if there is another secondary cause of hypertension because I have seen primary hyperaldosteronism with renal vascular hypertension together. So, he may have renal artery stenosis on top of ADPKD. You need to investigate further.

Dominiczak: I think that is a good suggestion. Something does not add up. This BP should have gone down. If you are not succeeding in a young patient, is there another diagnosis? Diagnostic tests again.

Alwakeel: Now this patient has 4 drugs, and he is not responding. So, I would look for resistant hypertension, consider poor compliance with his drug therapy, and monitor ambulatory BP to be sure that we really are facing high BP and not just office hypertension. I would go back to all these steps for somebody that is not responsive to medication. I would also

review if the patient is taking any other drug from any other physician to be sure we are really facing uncontrolled hypertension.

Dhaun: I will comment on the adherence issue. Although we cannot be 100% sure that he was adherent, he was engaged in his management. He kept 3 times daily BP records on his iPhone. He would text us using eMedicine and tell us that his drop was this or his drop was lacking and what symptoms he had. So, I would suspect that he was adherent to his drug regimen, although I could not guarantee that.

Van den Born: The option of reintroducing ramipril seems appealing to me, in a lower dose perhaps. You previously showed that it is effective. Perhaps a bit too effective in controlling his BP. Perhaps you should just reintroduce ramipril at a lower dose, which through its action at the efferent arterioles, will lower glomerular pressure. In the long run, this will hugely benefit his already worse kidney function.

Additional Investigations: Renal Angiography

We agree with all of your suggestions; given the resistant hypertension and the previous decline in his renal function with ACE inhibition, we opted to investigate for renovascular disease. The patient had a magnetic resonance angiogram. There was a stenosis near the origin of the left renal artery, and there was a suggestion of a small stenosis at the origin of the right renal artery as well (Figure 3A). A conventional dye angiogram confirmed the presence of a 9 mm stenosis in the proximal portion of the left renal artery with prestenotic and poststenotic dilatation (Figure 3B). The right renal artery looked normal on the dye angiogram.

The differential diagnosis of a lesion like this includes atherosclerosis, fibromuscular dysplasia (FMD), large vessel vasculitis, and a group of more unusual conditions, such as segmental arterial mediolysis.^{13,14}

Vlhahakos: I do not know his history. His arteries look ok. I don't think he has atherosclerosis. Could be something else.

Dhaun: The patient had no significant cardiovascular risk factors. He was a nonsmoker, fit, no evidence of atherosclerosis elsewhere in his vessels.

Dominiczak: From the shape of the vessel, although he is a man, it must be FMD.

Hunter: We felt this was FMD. It is worth noting that the radiologist commented that the iliac arteries were unusually torturous for a man of his age. Tortuosity of the medium and large arteries is associated with FMD.

Fibromuscular Dysplasia

FMD is reasonably prevalent, at least in a clinically silent form. The estimated prevalence of renal artery FMD in the general population is 4% (taking data from series of potential kidney donors and the Cardiovascular Outcomes in Renal Atherosclerotic Lesions [CORAL] study). However, most of that is clinically silent. It is more common in women (91% patients with FMD at all anatomic sites). It can present at any age, and it is associated with a variety of other vascular malformations, including tortuosity of medium and large arteries.^{13,15}

Historically, it was treated surgically and therefore classified histologically. In contemporary practice, it is often treated and diagnosed radiologically and is therefore classified on those grounds. The more common variant of the disease is

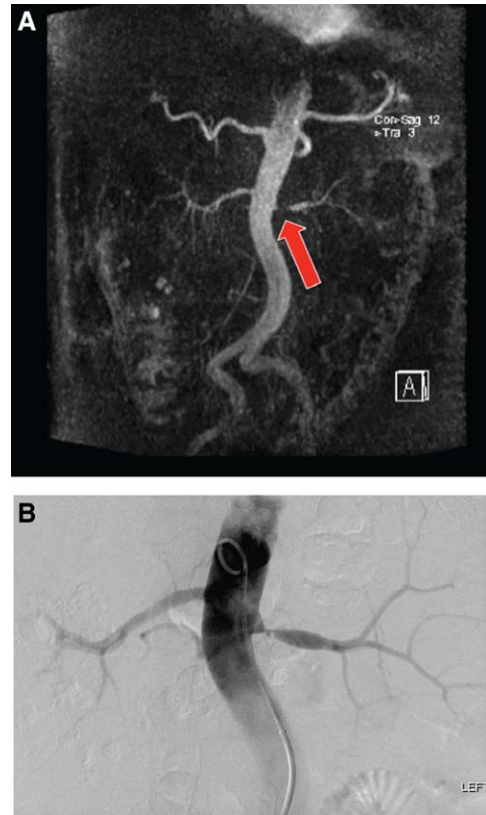


Figure 3. Angiographic studies. **A**, Magnetic resonance angiogram; 2-dimensional (2D) projection of 3D reconstruction. The arrow points to a stenosis in the proximal third of the left renal artery. **B**, Conventional dye angiogram performed via a catheter introduced into the femoral artery. A stenosis is visible in the proximal third of the left renal artery.

multifocal and gives a string of beads appearance on angiography, which arises as a result of alternating regions of stenosis and interstenotic dilatation. That tends to occur in the distal 2/3 of the renal artery and is almost exclusively found in women. In 20% of patients, there is a unifocal variant of the disease, which can affect any segment of the renal artery, tends to present younger around 30 years of age, and the ratio between the sexes is closer to unity.^{13,15} This fits with our patient.

Discussion: Management of Renal Artery FMD

Alwakeel: In the new investigation, 1 clue that this patient has renal artery stenosis is that when he was put on an ACE inhibitor the creatinine rose. So, when giving an ACE inhibitor causes the creatinine to rise we should always rule out renal artery stenosis?

Dhaun: I think the problem was the timing of the ACE inhibitor introduction given that we thought we were still in a period of acute kidney injury. What is important here is this patient has underlying significant CKD. We now know the patient has ADPKD with CKD. His BP is uncontrolled. He is currently not receiving any renin-angiotensin system blockade. We have diagnosed him with angiographic renal artery stenosis, which we think is nonatherosclerotic, so we believe it to be FMD. This would be an unusual cluster of diagnosis within this patient demographic. What do we do now? Some people in the renal community might accept his current BP

of 160/100 mmHg. There are patients with readings much higher than this. One option is to do nothing. Other options are to institute medical measures (such as enhancing his anti-hypertensive medication) or to intervene with angioplasty. To answer the question you need to decide what is the goal?

Dominiczak: You are at the hypertension meeting. Doing nothing with BP 160 systolic is not an option!

Gikonya: We know there is also angioplasty, which is not 100% corrective for BP, but I think for this particular patient we should consider it. My concern was on the arteriogram that you did. I am wondering with such a good picture on magnetic resonance imaging angiography the risk of the dye on kidney function, could we have avoided that and moved on only to the point where we need to angioplasty?

Dhaun: That is a good point: one should consider the potential for radiocontrast-induced nephropathy, particularly in a patient with CKD. However, although his serum creatinine was significantly elevated, his renal function was actually pretty good. His GFR was around 80 mL/min, and I think in that context, provided he was adequately hydrated, radiocontrast should be safe. The radiologist in particular was keen to do formal angiography because it was such an unusual magnetic resonance angiogram. It helpfully demonstrated (left-sided) unilateral disease (whereas the magnetic resonance angiogram had suggested a lesion on the right side also).

Alwakeel: In general, the intervention for FMD is angioplasty. I think in somebody who is on many medications for the sake of future management I'd go for angioplasty for this patient. I would inform him about the complications of contrast and side effects.

Dominiczak: Could we have hands up of everybody in the room who is a clinician and who would like to do angioplasty in this patient? (Vast majority of hands raised.)

Dhaun: All of you who raised your hand, could I ask: what is the goal of intervention? Is your aim BP control?

Audience: BP and preservation of renal function.

Dhaun: Would anybody not do angioplasty? I appreciate you might have to be brave given the number of hands that have just been shown.

Jennings: If this were atherosclerotic, I would be saying medical therapy. But because it is FMD, things are different.

The second thing is yes, BP control would be highly desirable but also the ability to use ACE inhibitors or ARBs without any constraint would be a useful outcome in itself.

Dhaun and Hunter: An excellent point.

Abu-Alfa: Just to follow-up on this last comment. The CORAL and other trials should not be coloring our decision, as this is a different disease. What was the gradient across the lesion?

Hunter: We did not measure that. We are aware that some centers do measure the pressure gradient to select those cases likely to benefit from angiographic intervention.

Abu-Alfa: Looks like the pressure gradient would be significant from the dilatation post stenosis.

Conservative and Interventional Therapy for Renal Artery FMD

A consensus of expert opinion suggests that best medical management of FMD comprises antiplatelet therapy (particularly for cerebral FMD), ACE inhibition with standard BP targets, smoking cessation, and possibly statin therapy.¹³ Because of the rarity of the disease, there are not any adequately powered RCTs to guide clinical practice.

The same could also be said of angioplasty. However, although there is no RCT on the scale of CORAL¹⁶ or Angioplasty and Stenting for Renal Artery Lesions (ASTRAL)¹⁷ (both trials in atherosclerotic renal artery stenosis), there are a lot of good observational data, mostly retrospective. A systematic review and meta-analysis in 2010 found that hypertension cure rates after angioplasty in renal artery FMD were reasonably good (27% to 46%). Despite short duration of follow-up, restenosis rates were significant (10% to 25% at 1–2 years).¹⁴ Importantly, and this has been factored into the decision in this case, there were better outcomes in younger patients with focal disease.

The patient went on to have angioplasty. The initial attempt made via the femoral route was unsuccessful, providing further evidence of vascular tortuosity. A second attempt made via transbrachial route was successful and elicited a diuresis of 21 L in the first 24 hours, confirming that this was a hemodynamically significant lesion. We did not deploy a stent. Over the 3 years since the procedure his renal function has remained

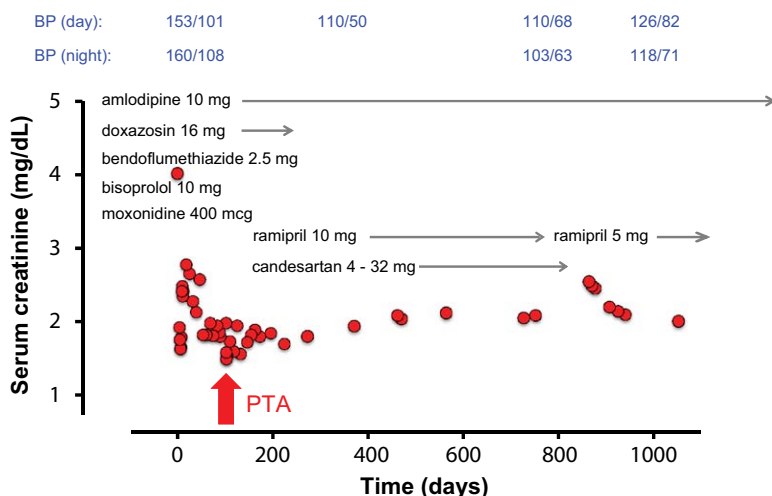


Figure 4. Clinical progress and response to percutaneous angiography (PTA). The serum creatinine is plotted over a period of >3 years. Home blood pressure (mmHg) and antihypertensive therapy are shown.

stable (Figure 4). All available data suggest that the procedure makes no difference to renal outcomes but hypertension is treated.¹⁴ His BP did improve to 110/50 mm Hg on amlodipine, ramipril, and candesartan relatively soon after the procedure.

Discussion: Dual Renin–Angiotensin System Blockade

Dominiczak: Why do you combine sartan and ACE inhibitor? What is the rationale?

Dhaun: I appreciate the results of Ongoing Telmisartan Alone and in Combination With Ramipril Global Endpoint Trial (ONTARGET),^{18,19} and I think it was useful in the cohort of patients it studied. However, in those patients who have proteinuria but who do not have diabetes or cardiovascular risk factors, it is not clear whether dual renin–angiotensin blockade impacts on long-term renal function, cardiovascular morbidity and mortality. In this patient, we did not at the time have the benefit of HALT-PKD, which compared ACE inhibitor alone with dual blockade in ADPKD. So the rationale for combining the 2 was maximum renin–angiotensin blockade because as you know you get ACE escape and the angiotensin II reactivation, and this system is known to stimulate cyst growth within the PKD cohort.

Summary

We present a case of accelerated hypertension and renal failure in a young man. The diagnosis was ADPKD and renal artery FMD. BP was controlled to target levels following percutaneous angioplasty and subsequent renin–angiotensin system blockade; renal function remained stable.

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Disclosures

None.

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