

## Elective Project Report

I spent my elective at The Royal Free Hospital, London doing renal medicine. I decided to undertake my elective in renal medicine for two reasons: 1) I am very interested in this specialty and am very strongly considering a career in it; 2) I had not had much exposure to renal medicine during my prior time as a medical student and I wanted to gain further experience of this specialty. During this elective I experienced the wide variety of renal medicine. I spent time on the wards and in the intensive care unit seeing acutely unwell patients with a wide range of renal pathologies, in satellite haemodialysis centers, in outpatient clinics, in theatre observing renal transplantation and in the pathology laboratories and meetings, where renal biopsy slides were prepared and discussed, respectively.

During this period I also assisted in setting up a patient database for a clinical research project on Autosomal Dominant Polycystic Kidney Disease (ADPKD). The project involved establishing a database of 396 patients with ADPKD who are under the care of the renal team at The Royal Free. It contained important information about their medication, imaging, blood test results and other clinical features. This database has been set-up in order to allow audit of the treatment and study of markers and predictors of progression in patients with ADPKD. This is going to tie-in with established research studies on urine and circulating biomarkers that are underway in the laboratory at the University College London Centre for Nephrology, which is also based at The Royal Free Hospital.

ADPKD is one of the most common genetic disorders, with an incidence of 1 in 400 to 1 in 1000. It is the fourth leading cause of end-stage renal failure (ESRF) in adults worldwide (Torres et al., 2007). ADPKD is characterized by large kidneys, pain, hypertension and, eventually, ESRF. Extra-renal manifestations include berry aneurysms in the circle of Willis (which can rupture and cause subarachnoid haemorrhage), mitral valve prolapse, hepatic cysts, pancreatic cysts and diverticular disease (Braun, 2009).

Diagnosis of ADPKD is based on the Ravine ultrasonographic criteria (Ravine et al., 1994) (please see table below):

Age	Positive Family History	Negative Family History
<30 years	2 cysts bilaterally (or unilaterally)	5 cysts bilaterally
30-60 years	4 cysts bilaterally	5 cysts bilaterally
>60 years	8 cysts bilaterally	8 cysts bilaterally

ADPKD is due to mutations in one of two genes, *PKD1* (located on chromosome 16) and *PKD2* (located on chromosome 4), which code for the linked transmembrane proteins polycystin-1 and polycystin-2, respectively (Grantham, 2008). Polycystin-1 and polycystin-2 are found on the primary cilium that is present on almost all renal tubular cells and collecting ducts. Polycystin-1 is expressed predominantly in the distal convoluted tubule and collecting ducts, and polycystin-2 is expressed predominantly in the distal convoluted tubule and

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loop of Henle. In the normal kidney, polycystin-1 and polycystin-2 are found on the surface of the primary cilium and act as mechanoreceptors regulating calcium entry. Influx of calcium into these cells helps to activate intracellular pathways that inhibit cell proliferation. In ADPKD, there is insufficient or abnormal polycystins and impaired calcium entry, which leads to unopposed activation of proliferative cell pathways. This causes cyst formation and ultimately leads to ESRF (Arnaout, 2001). Patients with polycystin-1 mutations are more likely to progress to ESRF earlier than those patients with polycystin-2 mutations.

Until recently, effective treatment for ADPKD has been lacking. Management of ADPKD has been reliant on meticulous blood pressure control (using angiotensin converting enzyme inhibitors (ACEi) and angiotensin II receptor blockers (ARB)) as the cornerstone of management. Avoidance of smoking and amelioration of other modifiable cardiovascular risk factors, in order to prolong kidney function for as long as possible are also important. Once ESRF is reached, treatment of these patients is with dialysis (peritoneal or haemo-), or by kidney transplantation.

Laboratory studies have shown that the antidiuretic hormone arginine vasopressin (AVP) and its second messenger adenosine-3',5'-cyclic monophosphate (cAMP) stimulate renal cyst proliferation and luminal fluid secretion (Gattone et al., 1999). Practical ways to inhibit AVP include drinking large volumes of water (in order to inhibit AVP release from the pituitary) (Nagao et al., 2006), and blockage of the AVP V<sub>2</sub>-receptor that is expressed in the distal convoluted tubule and collecting ducts using a group of agents called vaptans (Wang et al., 2008 and Meijer et al., 2011). A recent phase III multicenter, double blind, placebo-controlled trial involving 1445 patients with ADPKD compared tolvaptan, an AVP V<sub>2</sub>-receptor antagonist against placebo. The results showed that patients on tolvaptan, compared against placebo, had slower rates of increase of total kidney volume, and had lower rates of worsening kidney function and kidney pain (Torres et al., 2012).

Currently, investigations are on going in order to further delineate which patients with ADPKD are most likely to progress rapidly to ESRF. It is these patients that, theoretically, will derive the most benefit from tolvaptan therapy.

My project involved retrospectively looking at the electronic medical records and imaging of the 396 patients under the care of The Royal Free who were labeled as having a diagnosis of ADPKD. The patient records were accessed via Vital Data, a database containing information on all of the renal patients at The Royal Free, and the picture archiving and communication system (PACS), a medical imaging database that contained all of the scan results of the patients. The new ADPKD database was set-up, also using Vital Data, and included the following information: last clinic visit, history of a cerebrovascular event, presence of a known intracranial aneurysm, history of urinary tract infection, history of renal stones, previous nephrectomy, whether the patient is taking an ACEi or ARB or not (and the date the ACEi or ARB was started), smoking status, whether the patient has received any renal replacement therapy (dialysis or

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transplant) or not, and the length and volume of the kidneys when they were last imaged.

During this period of data entry, certain problems were encountered that will need rectifying. For some reason, I was unable to enter smoking details onto Vital Data. Some patients had not had a scan detailing renal length and volume. Some patients had had their renal size assessed by a CT kidneys, ureters and bladder and I was unable to enter this imaging mode onto Vital Data. The only two imaging options available for me to select were ultrasound and magnetic resonance imaging.

Further information that cannot be derived from electronic correspondence is going to be added to the database during clinic appointments and will include: symptoms (loin pain and macroscopic haematuria), family history (parents or siblings with chronic kidney disease, family members with berry aneurysms and offspring with ADPKD) and the research samples the patients have provided for laboratory analysis.

138 patients had no data entered onto Vital Data because of the following reasons: no records were available (48 patients), a diagnosis of ADPKD had not been made (24 patients), there had been no review in clinic for more than 2 years (68 patients), patient records had been duplicated (2 patients).

In the future, the database will be helpful as it will enable clinicians to easily assess the rate of cyst progression, as the results of renal lengths and volumes from previous scan results. A recent study evaluated a range of biomarkers found in the urine of 102 patients with ADPKD and showed that levels of proteins associated with glomerular (immunoglobulin G), proximal tubular (kidney injury molecule 1, N-acetyl-beta-d-glucosaminidase, neutrophil gelatinase-associated lipocalin and beta-2-microglobulin) and distal tubular (heart-type fatty acid binding protein) damage were raised in the urine of patients with ADPKD. More generalized inflammatory markers such as monocyte chemotactic protein 1 and macrophage migration inhibitory factor were also raised in the urine of patients with ADPKD. Furthermore, effective renal blood flow and measured glomerular filtration rate were associated with urinary excretion of beta-2-microglobulin, neutrophil gelatinase-associated lipocalin and heart-type fatty acid binding protein independent of urinary albumin excretion, while total renal volume was associated with kidney injury molecule 1, neutrophil gelatinase-associated lipocalin and monocyte chemotactic protein 1 independent of urinary albumin excretion (Meijer et al., 2010).

Hopefully, a correlation will also be found between further biomarkers in the blood and urine of these patients and disease progression.

Overall, I thoroughly enjoyed my 8-week elective in renal medicine and it has definitely enhanced my desire to pursue this specialty in my further career. In addition to setting up the ADPKD database, I gained a good grounding in renal medicine and enhanced my knowledge of day-to-day management of patients with renal disease. I would like to thank Dr David Wheeler for being my overall

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