Summary of Kidney Research UK funded ADTKD-UMOD patient day held at Freeman Hospital, Newcastle on 20 July 2024

Summary written by ADTKD RDG patient representative Angela Watt

Day co-hosted by Holly Mallibard and John Sayer of Freeman Hospital

Introduction

Professor John Sayer opened the day by looking at the geographical spread of attendees. Although the majority were from the Northern area, it was great to see some who had travelled from further south to attend the meeting.

He then opened the discussion by asking what participants wanted to get out of the day. Suggestions of topics included

- Thinking about the next generation
- What age is a suitable age to undergo testing?
- Looking after your kidneys
- Learning from each other
- Information on the condition
- New treatments
- Genetics

Session 1 - ADTKD-UMOD Basics

Dr Holly Mabillard began by clarifying that the name for the condition was only agreed a few years ago. It was previously known as

- Medullary cystic kidney disease type 2
- Familial juvenile hyperuricaemia nephropathy type 1
- Uromodulin-associated kidney disease

AD – Autosomal Dominant – describes how the condition is inherited

T – Tubulointerstitial – refers to the part of the kidney it effects, the area where salt and water are exchanged

There are seven categories of ADTKD. They are categorised according to the mutation they cause. In this condition the gene is called UMOD.

What does the UMOD gene do?

It makes a protein called uromodulin in the kidneys. Uromodulin is secreted into the kidney where it forms a gel like structure. This gel protects the kidney from bacteria in the urinary tract, prevents the formation of kidney stones and stops salt from leaking into the kidney.

When there is a mutation in the UMOD gene, the DNA code makes faulty uromodulin. As the protein can't move into the urine, it builds up in the kidney and forms a scarring called 'fibrosis'.

ADTKD is classed as a rare disease. It effects 9/million people but is thought to be underdiagnosed. It accounts for 2% of people with CKD and 1% of people with CKD stages 3-5. It is the third most common inherited kidney disease.

Signs and Symptoms?

Most people will have a normal kidney size and no blood or protein in their urine.

GOUT

50% of women with the gene and 70% of men will have gout. This can occur at a young age and due to a build up of uric acid in joints.

CYSTS & SALT WASTING

Small kidney cysts may be present but are asymptomatic. This is uaually something mild such as an irregular kidney outline or a slight dilation of the cavity in the inner kidney through which urine passes. There is often evidence of salt wasting or loss early in the condition. Symptoms of this may include low blood pressure and feeling light-headed.

Children may have a history of bed-wetting.

KIDNEY FAILURE

The median (average) age of kidney failure is 47 years but this ranges from 18-88 years. Some with the mutation may never develop kidney failure. This is assessed by measuring creatinine in the blood and using this to measure the 'eGFR' which predicts the percentage of kidney function remaining. Dialysis is usually necessary when this reaches around 6%. Symptoms will include

- Shortness of breath
- Tiredness
- Loss of appetite
- Swelling in the feet and ankles
- Nausea and vomiting
- Weight loss
- Headache
- Itch
- Bad breath

ADTKD can affect both men and women. It does not skip a generation, but family members can present with different symptoms. It is diagnosed using a genetic test which is usually taken from a blood sample but can be a cheek swab.

DIAGNOSIS

This is performed by taking a family history. Other tests may include a urinalysis and an ultrasound scan and blood will be taken for genetic testing. A biopsy is not necessary for diagnosis if the genetic test is positive. Having a genetic result is also important for future trials into the condition.

TREATMENT

Losartan is the medication most recommended for lowering BP and reducing the amount of protein in the urine although others from the same class of drug may be prescribed.

Slow sodium may be prescribed to help symptoms of salt wasting.

Medications such as allopurinol or febuxostat can be prescribed to treat symptoms of gout.

ADTKD does not recur after kidney transplant as the new kidney will make its own unaffected uromodulin.

RESOURCES

RaDaR Registry | The UK Kidney Association RaDaR is a registry of all patients in the UK with a rare kidney disease. You may have been recruited to it by your local kidney team. It is overseen by the UK Kidney Association. As well as providing data on how people with rare kidney conditions present and what happens to them, it also allows researchers to contact you with any research opportunities that may be relevant to you.

Home | Kidney Research UK The UK's largest charity funding research into kidney disease.

Kidney Care UK, the UK's leading kidney patient support charity | Kidney Care UK A UK based charity providing support to patients and families affected by kidney disease.

National Kidney Federation UK based organisation which is an umbrella organisation for the regional kidney patient associations, providing support and guidance.

Rare Kidney Disease Foundation Based in the USA but dedicated to ADTKD

ADTKD Self-Help Rare Kidney Disease German organisation

There is also an annual ADTKD international summit. Sessions are available to join online.

Genetcs – What You Need to Know

Dr Lorraine Cowley – clinical/academic genetic counsellor gave this presentation. Her role is mainly a clinical role and she is mainly works in genetic kidney diseases. This involves

- Finding an underlying cause for kidney diseases
- Compiling a family tree
- Deciding who it is appropriate to test
- Helping those referred for testing to make informed decisions
- Arranging screening

Academically, Lorraine's PhD looked at patient and family perspectives of genetic screening.

Genes can be seen as the recipes for making proteins in the body. Some changes to a gene can be 'benign' and won't have an effect. Some changes may be classed as 'pathogenic' and will cause disease.

We have around 20,000 pairs of genes – one of each pair inherited from each parent.

Dominant inheritance like in ADTKD, means that if one parent carries a genetic mutation, there is a 50% chance of passing it on to their child. Predictive testing is performed on anyone with a 50% chance of inheriting or if they are symptomatic.

Points to consider before undergoing genetic testing

- Need for health monitoring
- Lifestyle – career, insurance, travel or living abroad
- Emotional response
- Is it the right time?

Options for future generations

- Have children naturally
- Pre-implantation testing. This uses IVF. Cells from the embryo are tested for UMOD mutations and only embryos without the mutation are implanted. Currently only available in Nottingham or London.
- Pre-natal testing. A sample is taken from the placenta around week 11 of the pregnancy via a biopsy taken under the guidance of ultrasound. If the result is positive, then a termination would be offered.

Research Update

Dr Holly Mabillard led this session.

There are a number of characteristics of ADTKD that must be taken into consideration when carrying out research but international collaboration can assist this.

- The nature of rare diseases makes it difficult to recruit enough patients to power a study
- The condition was only fully characterised in the early 2000s
- There are 135 known UMOD genetic changes or mutations
- ADTKD is almost 100% penetrant (penetrance refers to the percentage of people with the mutation who will get the disease)
- In the UK most patients have the same mutation but there is less gout seen than elsewhere
- Some mutations are associated with a faster decline of kidney function
- The age at which kidney failure occurs differs even within families
- We still need to understand more about why the scarring occurs
- Why do people suffer different symptoms?

Harvard University has recently completed a drug screen using 'organoids' – kidney cells grown in a lab which have a MUC1 mutation – also known to cause ADTKD. They have found a compound labelled BRD4780 which has been shown to reduce the amount of UMOD that gets stuck in the kidney. The next step would be clinical trials.

In Newcastle the team are using data from RaDaR to look at patterns of the disease in the UK. They are also studying kidney cells obtained from the urine of patients with ADTKD. This avoids using animal models for experimentation.

Dr Mabillard's PhD is looking at why there are differences within families. She is looking at 'modifiers' withing the DNA that can account for this and for potential treatments for future targets. She is also hoping to find a biomarker in the blood or urine of affected patients that could predict progression. This could potentially lead to involvement from the pharmaceutical industry.

How Can You Help?

- Ensure you are recruited into RaDaR and to receive notifications from them should a clinical trial open
- Register on Home | ClinicalTrials.gov to receive notification of other clinical trials
- Raise funds towards future research. Kidney Research UK had a dedicate UMOD Research Fund that is ringfenced for research into this condition

- Setting up a UK based patient group. If you would be interested in helping with this or being a part of it contact holly.mabillard2@newcastle.ac.uk. Suggestions are also welcome as to what format this group should take, what it should do and how it should communicate eg. Facebook, email?

How to Look After Your Kidneys

Dr Holly Mabillard presented this session on the best way to look after your kidneys. Although your genes are something you inherit and can do nothing about, there are a number of lifestyle issues that you can control.

Diet

For general health, poor diet is a greater risk than smoking. Ultra-processed foods can increase your risk of ill health. (Ultra-processed foods are those containing ingredients that you wouldn't usually find in your kitchen.) A diet rich in fibre can also decrease your risk of diabetes, cardiovascular disease and some cancers.

Renal dieticians will provide more tailored support if you have a decline in kidney function but other things you should consider are moving towards a more plant-based diet, decreasing salt intake, DASH diet (Dietary Approaches to Stop Hypertension.)

Exercise

Resistance exercise is aimed at maintaining muscle mass. It can slow the decline in kidney function, reduce the risk of diabetes, reduce inflammation and improve blood pressure control.

Cardiovascular exercise can increase blood flow and therefore oxygen supply to the kidneys and also help to reduce blood pressure and inflammation.

The best method of exercising is to find a combination of both resistance and cardiovascular.

Sleep

Sleep helps to reduce your heart rate and blood pressure. It also allows the body to regulate your hormones, remove waste and toxins from the brain, produce immune cells and release growth hormones. 7-8 hours per night is the optimal sleep time for someone with CKD. Sleep disturbance can increase kidney damage, increase inflammation and insulin resistance.

To assist with a better sleep pattern, try to sleep in a dark, cool room and avoid evening light and caffeine.

Medications

Avoid all drugs classed as NSAIDS (non-steroidal anti-inflammatory drugs) such as ibuprofen. Doses of some medications may also need to be reduced if you have impaired kidney function. Speak to your kidney team before taking any herbal medicines or supplements. Make sure you are aware of 'sick day rules' if taking any medications known as ACEIs (usually ending in 'pril') or ARBs (using ending in 'tan').

General advice

- Stop smoking
- Reduce alcohol intake
- Stay well hydrated if you haven't been told to restrict your fluid intake

- Maintain good oral health
- Beam Feel Good provides health and well-being and exercise sessions specifically for people with kidney disease
- There are also several podcasts around kidney disease

Kidney Clinics and Renal Replacement Therapy

Matron Glenda Bestford is Deputy Matron for Renal Services and Sister Alison Malone is Senior Sister in the renal OPD & day unit at the Freeman Hospital. They presented this session and although they work in Newcastle, the information will be the same in all renal units.

Social and emotional support is a key part of their role. This is done by good communication, looking after 'the little things' that might compromise your care and putting you at the heart of your care.

Shared decision making is at the heart of the relationship between you and your kidney team.

Transplant

It is important to remember that a transplant is a treatment and not a cure. A transplant could be from a living donor (usually a relative or friend) or a deceased donor from the waiting list. Your kidney team can discuss both these options with you.

Haemodialysis

This is a method of cleaning the blood and removing fluid - things normally done by your kidneys. Blood is removed from your circulation through a circuit and a filter using a machine and then returned to you. It is normally carried out for around 4 hours, 3 times per week. With training you could carry this out at home. Speak to your kidney team regarding this.

Peritoneal dialysis

PD is carried out by the patient at home although loved ones can be trained to assist. This was described as using a 'tea bag effect'. A permanent tube is inserted into your tummy, the end of which sits behind the peritoneal lining. Fluid is drained into the space and osmosis and diffusion are used to remove toxins and excess fluid.

CAPD (Continuous Automated Peritoneal Dialysis) is carried out 4 times per day and each 'exchange' will take about 30 minutes.

APD (Automated Peritoneal Dialysis) is carried out overnight by attaching to a machine while you are sleeping. It takes around 6-8 hours.

Mustard Stories

In addition to the above sessions, the team from Mustard Stories also ran 2 workshops during the day. Theses were centred around patient journeys and stories and the work gained from them will assist in providing evidence of patient experience for future research proposals.