Improving prediction of disease outcomes and treatment options in childhood steroid-resistant nephrotic syndrome

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Background

Normally your kidneys work like a specialised sieve to filter out small waste products while keeping larger substances, like proteins, in your blood. If your kidneys become leaky, proteins pass into your urine and fluid builds up in the wrong places in your body. This leads to swelling of your face and other areas. This is called nephrotic syndrome and is a disease mainly affecting children.1 Standard treatment is with steroids and although they work in most children, for about one in five they do not. This is known as steroid-resistant nephrotic syndrome (SRNS). Among this group, many patients develop kidney failure needing dialysis and eventually a transplant. Unfortunately, in some children the disease comes back in the new kidney after a transplant.

We know from previous research that in nephrotic syndrome the normal shape of specialised kidney cells, called podocytes, is disrupted. This leads to breakdown of the slit-like barrier and loss of protein in the urine (Figure 1).2 SRNS has several different causes. In about one third of patients it is a genetic disease. In these cases it is caused by defects (mutations) in one of more than 30 genes which control how podocytes work.3 In the other cases, the cause of disease is unknown but it may involve proteins released into the patient's blood from cells of their immune system.

Testing for genetic mutations and measuring levels of proteins in blood could help to separate patients with SRNS into groups which respond differently to treatment. Characteristics, such as genes or proteins, that can be measured and linked with disease are called biomarkers. Journal articles have highlighted that the development of biomarkers will be important for improved treatment of kidney diseases.3

Our Research Questions

At the moment we do not have good ways to predict which children with SRNS will develop kidney failure and which will respond to particular treatments. If we could identify high-risk and low-risk patients we could better target therapy and take actions to minimise the chance of disease recurrence after transplant. The important research questions are:

• Can we identify early in the disease which patients will progress to kidney failure, transplant and recurrence?

• Which patients respond to which treatments?

• What biomarkers may help with predicting this?

• Can we develop a treatment pathway based on clinical features, genetics and blood tests?

Methods

• The UK National Registry for Rare Kidney Diseases (RuDKiD): Since 2010 we have collected data about patients with a range of kidney diseases. Initially we focused on children with SRNS but have now expanded to include adults and those with steroid-sensitive nephrotic syndrome.

• The National Study of Nephrotic Syndrome (Nephro5): We have collected blood samples from patients for genetic (DNA) testing to look for known and new genes that cause SRNS.

• So far we have analysed over 180 patients to see if they have genetic disease. We checked all their genes in a process called whole exome sequencing. We also looked at whether they progressed to need a transplant and had recurrence of disease afterwards.

• We have used previous research from our group4 to develop a test of 37 genes thought to cause SRNS.5 Since May 2013, this test has been available through the NHS Genetics Service at Bristol Genetics Laboratory. We have looked at the results from patients tested between May 2013 and July 2015 to see how many have a genetic disease.

Results

Figure 1: The kidney filter with normal podocytes (left) and disrupted podocytes (right)

The kidney filter has three parts: (1) Podocytes sit next to the urine and are linked together by slit diaphragms (SD). (2) The glomerular basement membrane (GBM) is a meshwork which supports the cells. (3) Endothelial cells sit next to the blood. Normally red blood cells (rbc) and proteins like albumin stay inside the blood (left picture). In nephrotic syndrome, albumin leaks into urine (right picture). Adapted from: Ronco P. (2007)7

Figure 2: Age of disease onset in SRNS patients with or without causative genetic mutations (total number = 188)

Figure 3: Transplantation and subsequent recurrence in SRNS patients (total number = 188)

At 15% of children with non genetic SRNS

Figure 4: Outcomes after transplant according to type of steroid resistance (SR) (total number = 184)

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Our research is ongoing and we now have over 1300 patients with nephrotic syndrome recruited into RuDKiD. Our current projects are:

• To look at responses to drug treatments other than steroids. We will compare patients who respond and those who do not and with different patterns of steroid resistance.

• To carry out more detailed genetic testing using whole genome sequencing (looking at all a patient's DNA).

• To measure levels of proteins in patients' plasma (the liquid part of blood). We will compare times when patients develop disease and when it is well controlled. We hope to identify biomarkers that can help with treatment.

References


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