PRACTICE

A PATIENT'S JOURNEY

Living with alkaptonuria

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This is one of a series of occasional articles by patients about their experiences that offer lessons to doctors. The *BMJ* welcomes contributions to the series. Please contact Peter Lapsley (lapsley@bmj.com) for guidance.

Simon Laxon, who was diagnosed with a rare genetic disorder, alkaptonuria, soon after birth, describes his journey in understanding the condition and finding hope for a cure

I was born in 1966, and within a few days of my birth my parents knew that something was wrong. There were dark purple stains in my nappies, so my mother took me to a consultant at my local hospital for investigation.

After a meeting of specialist doctors, one of my nappies was sent for tests. The doctors suspected porphyria, but the test came back negative. A urine test led to the discovery of a rare genetic disorder. The doctors explained it would cause a type of arthritis: not crippling like rheumatoid arthritis, but one that would cause aches and pains as well as turning the cartilage in my ears blue. My parents felt there was no need to worry, so I grew up fairly normally. I was quite athletic at school and trained several times a week.

In 1987 I developed a duodenal ulcer and had to go into hospital, where doctors rediscovered the genetic disorder (my original records had been lost). This time a name was put to it: alkaptonuria. The doctors knew little about it, but told me I would develop mild arthritis and that my urine would turn black if left to stand. We explained about the meeting of the specialists when I was only a couple of weeks old and the stained nappies. The doctors said that this was a symptom of alkaptonuria and was nothing to worry about, as the genetic defect was harmless.

It took me a year to overcome the ulcer. By this time I was starting to suffer with aches and pains in my lower back. I found that I could not get back into a physically active lifestyle because my body hurt so much after every attempt. At the time I did not realise how much damage this disorder would do to me.

I found that the pain and stiffness were starting to affect my work. I was a brake prototype engineer, working underneath

vehicles. I would spend a lot of time bending or crouching and noticed that my back became very stiff and ached to the point where I would have to stop work. If I sat down for a long period of time, I would not be able to stand up straight for at least 10 minutes because of the stiffness.

In 1997 I started to get severe pain in my lower back. My doctor told me to rest, but after the pain worsened he referred me to a specialist rheumatologist. I was sent for a radiograph of my back, which led to a diagnosis of degenerative disc disease. The rheumatologist told me nothing could be done and discharged me.

The pain still interfered with my job, so my works manager sent me to a private physiotherapist. After an examination the physiotherapist referred me to an orthopaedic surgeon, as he suspected ankylosing spondylitis. A few weeks later, I collapsed with intense pain in my lower back. I was taken to hospital and admitted for 10 days. A magnetic resonance imaging scan showed degeneration of the cartilage in my lower back. I was told again that the problem was mechanical back strain and degenerative disc disease and that nothing could be done. I was discharged from hospital but was unable to work—as a result I lost my job.

In 1998 I was invited to meet a geneticist, Victor McKusick, from Johns Hopkins University. He told me that alkaptonuria does cause early onset arthritis as well as a vast number of other problems. He took photographs of my ochronotic ear cartilage and explained that my black earwax was also due to alkaptonuria. He confirmed that it was to blame for the pain in my joints. Armed with this information I went back to my doctor who referred me to another rheumatologist.

My new rheumatologist had experience of treating patients with alkaptonuria, so he knew that my problems were connected. He wanted to see me every three months and take blood and urine samples for testing. A year later he retired and the rheumatologist who took over from him still treats me to this day. He is aware of the destructive nature of alkaptonuria and regularly sends me for blood, urine, and bone density tests.

In December 1998 my pain management doctor performed a spinal manipulation, which made the pain worse. We decided to look into spinal injections as an alternative. Since then I have had over six facet joint injections. These seem to ease the pain for an average of six months.

In January 1999 I started to feel unwell. I suffered more back pain and had trouble urinating. I was tested for infections but nothing showed up. I mentioned to the doctors that alkaptonuria could sometimes cause prostate stones. In May I went into hospital for a cystoscopy. My doctor managed to scrape some calculi from the surface of my prostate. They were probably caused by alkaptonuria. So far I have had two stones removed and regularly pass small, black, gravel-like stones.

In 2000 I was searching the internet for alkaptonuria research when I came across an article by Charles Scriver of McGill University in Canada. I made contact and he sent me a copy of the paper he had written on alkaptonuria. I kept in touch and found that another patient in the UK wanted to set up a website dedicated to helping those with alkaptonuria. He put me in touch with Robert Gregory, who is now the manager of the AKU Society in the UK. I signed up and have been a member ever since. Their aim, and that of Lakshminarayan Ranganath and his team at the Royal Liverpool University Hospital, is to find a cure for alkaptonuria.

I also came across the National Institute of Health (NIH) in the United States. They were looking for people to take part in a new study on nitisinone, an unlicensed drug that prevents the accumulation of the homogentisic acid that causes the damage in alkaptonuria. I contacted them and in February 2001 I flew out to the NIH. I spent the next week having a vast array of tests before flying home.

In 2004 I had arthroscopy on my knees. My orthopaedic surgeon told me that my left knee showed signs of ochronosis, but my right one looked normal. To date, I have had a further three arthroscopies and a meniscus repair.

In June 2005 I was asked to return to the NIH. This time I was to participate in the study of nitisinone and return every four months for follow-up appointments. While on nitisinone I felt normal again. All the pain seemed to disappear and the stiffness seemed to ease completely. I could play games with my children—something that I could not do before—and we were a normal family. This seemed to happen after being on the drug for only a week, and continued for the four years I was on it. I was deeply saddened when I received an email from the NIH saying that they were to stop the trial. It felt that this was the only hope that we had, as an AKU Society, and now that was gone.

Last year I travelled to the Royal Liverpool University Hospital to take part in their alkaptonuria clinical evaluation programme under Dr Ranganath, a consultant in metabolic medicine. I stayed at the hospital for three days while scans, radiography, and other tests were performed. Work like this is helping to advance medical knowledge about alkaptonuria. Without this glimmer of hope, future alkaptonuria sufferers face years of severe pain and joint replacements. We are hoping a cure will be found so that future generations will not have to go through what we have.

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A doctor's perspective

Alkaptonuria causes considerable morbidity in adulthood due to severe premature destructive spondyloarthropathy. It is a rare genetic disorder arising from a lack of homogentisate dioxygenase, the enzyme responsible for metabolising dietary phenylalanine and tyrosine through homogentisic acid (HGA). Because it is very rare—a prevalence of around 1 in 500 000 in most populations, including the UK—it is often missed or not considered at first presentation, as in this case. It is present at birth as dark urine and staining of nappies and can be confirmed by a simple laboratory measurement of HGA in urine. It is often considered a curiosity in children, and patients are sent away with false reassurance. Misleading and potentially detrimental advice can be given regarding diet, occupation, and lifestyle. Patients who are not followed up after diagnosis are often lost to the system—as were Simon's original records—which is problematic in a disease that causes severe disability in early adulthood. The initial diagnosis is an opportunity to screen siblings.

Most HGA is excreted by the kidneys. The remaining HGA is oxidised via benzoquinone acetic acid to a melanin-like polymer and deposited in connective tissues, a process termed ochronosis. By their late twenties most patients experience severe back pain, often accompanied by blue-black pigmentation of the pinna, with scleral pigmentation developing soon after due to progressive ochronosis. Progressive arthritic pain affecting large synovial joints (especially knees, hips, and shoulders) is also seen. The combination of back and joint pain, and pigmentation of the ear and eye with a background of black urine should alert a medical practitioner to a diagnosis of alkaptonuria.

Other than joint cartilage damage, manifestations of alkaptonuria include those due to high HGA (stones in kidney, prostate, gall bladder, and salivary gland), ochronosis (visible external pigmentation in eye, ear, skin, and teeth), and ochronotic tissue damage (pigment alters material properties of tissues, leading to ruptures of tendons, ligaments, muscle; bone fractures, as well as cardiac valve damage, also occur).

Current management of alkaptonuria is palliative, dependent on appropriate lifestyle choices and pain relief. Low protein diets and ascorbic acid are of unproven value as treatments. Effective analgesic management, physiotherapy to keep joints supple, and ultimately arthroplasty for total joint failure are required. There is a potentially effective HGA lowering treatment that does not involve gene or enzyme replacement. This agent, nitisinone, inhibits p-hydroxy phenyl pyruvate dioxygenase, the enzyme leading to formation of HGA. Despite its unequivocal lowering of HGA, and anecdotal descriptions of clinical benefit including pain relief—as experienced by Simon—there is no clinical trial evidence of its effectiveness. This is largely because the natural history of alkaptonuria is not well understood. Researching a rare disease to increase understanding and to develop effective treatments can be challenging. A well designed clinical trial exploring the potential of nitisinone in alkaptonuria is urgently required to alleviate this currently untreatable disease.

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Useful resources

AKU Society (www.alkaptonuria.info)—UK based support group for alkaptonuria patients, family, and carers. Founded in 2003 by Dr Ranganath and Robert Gregory. Communications project manager, Oliver Timmis oliver@akusociety.org

ALCAP (www.alcap.fr)—France based support group for alkaptonuria patients, family, and carers

AKU Society North America (www.akusocietyna.org)—USA based support group for alkaptonuria patients, family, and carers

AKU communities (www.rarediseasecommunities.org/en/community/alkaptonuria-aku)—an online community and support forum for alkaptonuria patients, part of rare disease communities, a joint project between EURORDIS and NORD