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# FAMILIAL JUVENILE HYPERURICAEMIC NEPHROPATHY (FJHN)

*A Guide for Parents and Professionals*

PUMPA

# Contents

# LIVING WITH FJHN

## A PATIENT'S VIEW

Lesley Kinge

My experience of the problem started at the age of 9 years, when my twin sister and I were taken into hospital for investigations because my sister had developed gout in her foot. I was found to have blood uric acid levels above normal too. Regular hospital visits started then, and I have attended hospital frequently ever since.

### Teenagers do not like taking medicines, but need to be persuaded!

I myself was reasonably well, but my sister had lots of problems with her joints. In 1968 at the age of 17 we were put on what was then a new drug called allopurinol, to help control our high uric acid levels and gout. Our parents had a hard job impressing on us how important it was to keep taking these drugs on a daily basis. Like all teenagers, we did not like having to take medicine frequently.

The first time we realized the seriousness of our problem was when our mother's twin sister died of renal failure at the age of 44. Our mother too died of renal failure at 47. This had a terrible effect on us as a family, but as time went by we slowly rebuilt our lives.

I was married 6 months later and at this point my sister and I attended for genetic counseling, which revealed to us that the disease was hereditary and had a 50% chance of being passed on to any children. It could also shorten our own lives, as in mother's case, and for these reasons we made the decision not to have children.

### Hopes raised by dialysis and transplantation but alas these were early days!

Seven years later we suffered another blow. My twin sister's health was deteriorating and by 1980 she was in severe renal failure. However as a result of medical progress

she had a chance of new life. This meant 3 days a week on dialysis, which would act as her new kidneys. Marvellous!

She could not stay on this machine forever, and so had the ultimate gift of life - a new kidney. In fact she had 3 such chances of life - the last one in 1989, but unfortunately all three kidneys failed, and she died at the age of 37, when she had been married for only 3 years.

In the same year my cousin, who had likewise been on dialysis for renal failure also had a life-giving kidney transplant which, thankfully, she still has today.

## How does FJHN affect the patient?

Kidney disease, like the one in our family, is associated with slow deterioration: feeling unwell, terrific tiredness - just to walk a short way can be exhausting - followed by painful joints, and when the kidneys start to show signs of failure you are put on a low protein/low potassium diet. That's hard! Most foods have some kind of protein and it seems when you cannot have it you want it!!! It also means a very controlled liquid diet. Whilst on dialysis, my sister was on half a pint a day taking into account liquid in food. When we went out socially she would have a glass of ice because in volume it was small.

Like myself, my cousin's daughters have the disease, but hopefully recognition and treatment with allopurinol was started sufficiently early and will keep their problem under control. Our hope is that one day the defective gene(s) will be found and future families like ours will not be **"PARENTS WITHOUT CHILDREN"**

# I - What is FJHN, and how do we diagnose it?

## WHAT EXACTLY IS FJHN ?

J Stewart Cameron

### What is FJHN ?

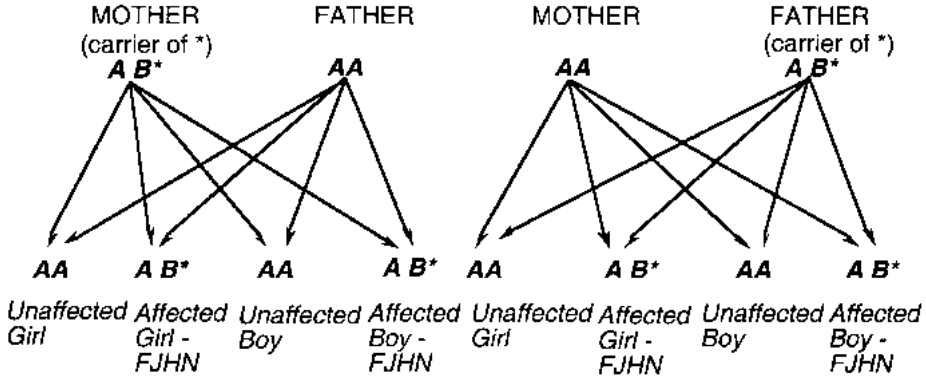
FJHN is the abbreviation used for a rather uncommon inherited disorder first described in 1960. This shows itself by high levels of uric acid/urate in the blood (hyperuricaemia) sometimes causing gout, and/or kidney disease.

### Why the initials FJHN?

- The F is for "*Familial*" indicating it is inherited - a disorder which runs in families and has a dominant inheritance. This means it is passed by one parent - an affected mother or father - to half their children whether male or female.

*Figure 1.*

### FJHN Passes via either parent to half their children




* gene for FJHN

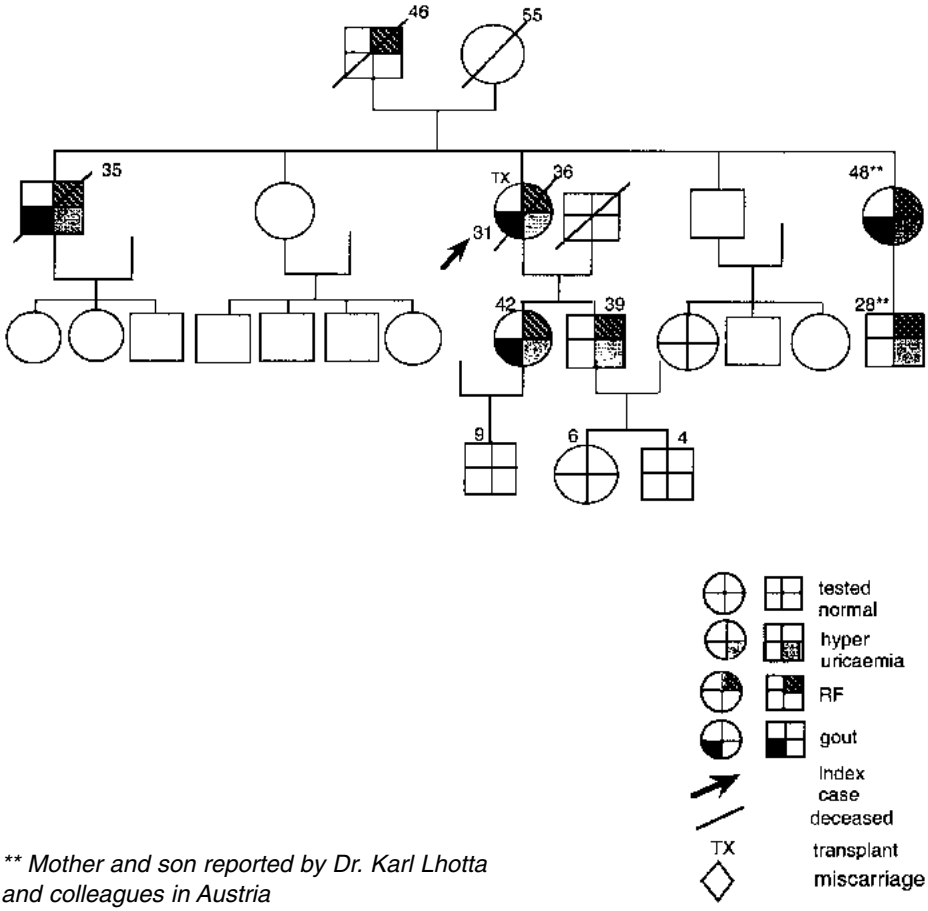
- The onset is often in childhood or adolescence, hence the J "Juvenile".
- Gout is not always present, but the level of uric acid is always raised (hence the H for Hyperuricaemia). This is most unusual in young people, but in FJHN may be

present even from birth which again is very unusual.

- The N is for nephropathy - the associated kidney disease. Finding or developing kidney disease, as happens frequently in this form of gout, is very unlike the well-known classical gout of middle-aged often over-indulgent males, who are overweight and may have high blood pressure, but in whom renal disease today is rare.

Thus the family history of FJHN is typical of a *dominantly-inherited* condition, with patients of either gender in consecutive generations showing various combinations of hyperuricaemia, gout and renal failure, as in this family:

*Kindred GB 1*




*** Mother and son reported by Dr. Karl Lhotta and colleagues in Austria*

*Affected brother and sister (right) in Kinsed GBI*

FJHN affects young men, young women and children equally (Figure 2). Also, as you can see from this picture (right) of an affected brother and sister with FJHN, people with this condition are often slender and have a normal blood pressure, at least in the early stages of the disease, both at variance from usual middle-aged male patients with "classical" gout. If unrecognized and untreated as happened in the past, kidney disease usually becomes obvious between 10-30 years of age, and progresses slowly to end-stage kidney failure within 10-15 years which may require regular dialysis treatment and/or kidney transplantation. The kidney failure is the result of chronic inflammation of the substance of the kidney (the interstitium), but only rarely have actual urate crystals been found on microscopic examination of kidney tissue.

Ultrasound scan examination of the kidneys usually shows only reduced kidney size with abnormal echo pattern. However, although seen in some other countries rather frequently, only one of our UK families so far have also had fluid-filled cysts in the inner part of the kidney, the medulla. This appearance is usually called **Medullary Cystic Kidney Disease (MCKD).** This group of patients with cysts often (but not always) show kidney failure and a high blood uric acid, and thus resemble FJHN closely, and MCKD also has a dominant inheritance. The exact relationship between the two conditions is not yet clear but they may show the same abnormal genes *(see Marinaki below).*

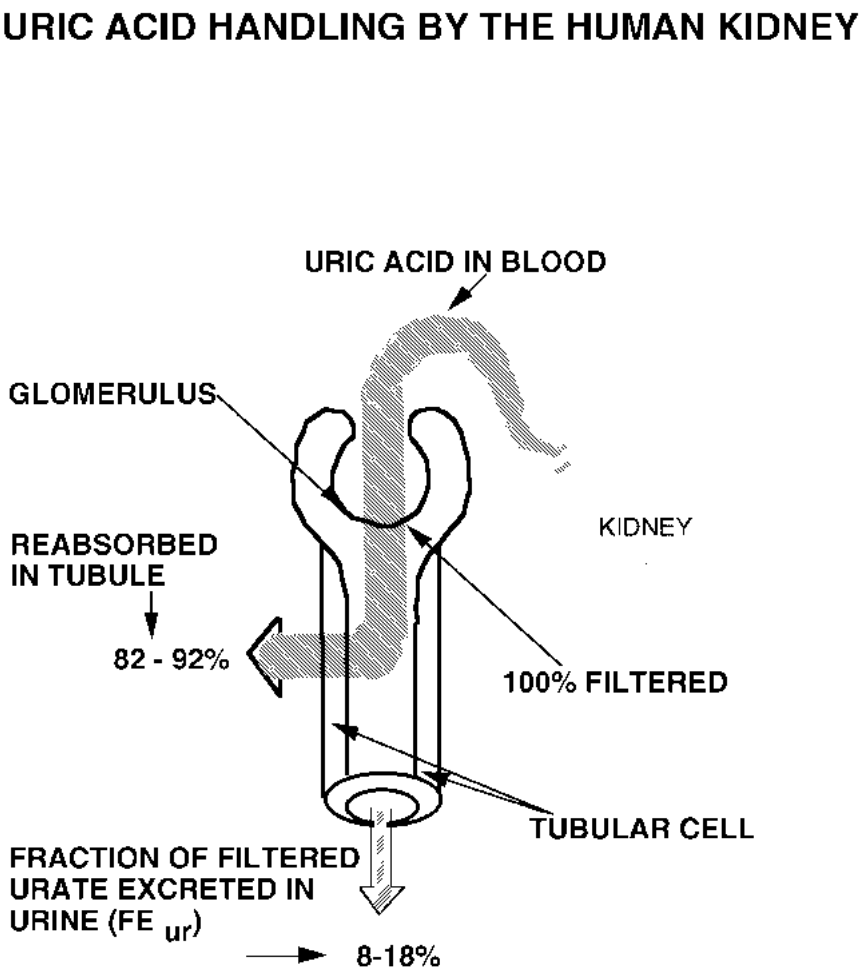
## How do we diagnose FJHN?

*(see Fairbanks and Marinaki below)*

Apart from clinical clues such as gout if present, there are clues from laboratory tests: two biochemical hallmarks distinguish FJHN: The first is a higher concentration of urate/uric acid in the blood than expected, allowing for age, gender and kidney function (all of which influence the plasma uric acid concentration). The second is a lower amount of uric acid in the urine than one would expect from the plasma uric acid concentration. This lower urate excretion is the cause of the rise in the blood urate concentration.

Normally, urate in the blood is freely filtered through the tiny filters (glomeruli) of the kidney, but approximately 90% of this filtered urate is then reabsorbed back in the kidney tubules as shown in Figure 3.

*Figure 3.*




Thus the fraction of **F**iltered urate **E**xcreted (called the $FE_{urate}$) by adults is normally around 10% (range 8-18%) of that for a marker substance like creatinine which is filtered only, not reabsorbed.

The $FE_{urate}$ is a little greater in women, and especially so in children (up to 30%) In contrast, the $FE_{urate}$ in people affected with FJHN is only 3-7 % of the clearance of creatinine in men, women - and even children.

## FJHN is the result of defects in several different genes

*(see also Marinaki further on)*

The fact that the low excretion of urate in FJHN is present in affected family members from infancy, before any other changes appear, suggests that a defect in the transport of urate in the renal tubule may be the culprit - but what gene or genes are involved in producing this low urate excretion?

One major gene is now known, which accounts for 1/3 to 1/2 of the affected families in the USA and Europe (and a few families in the UK) who suffer either FJHN or the related from of MCKD discussed above. This gene codes for a protein produced within the kidney and excreted in the urine, now called "uromodulin". Uromodulin has been a recognized urinary protein for 50 years, but its function was unknown. In the main group of FJHN patients with mutations in the uromodulin gene, uromodulin accumulates within the cells and clogs them up. How this relates to the increased re-absorption of urate is not clear yet. Other mutated genes have now also been found on chromosome 17 (*see Bingham below*) and on chromosome 1, while other families have none of these gene defects, so there must be yet more genes involved. Some patients with cysts in the medulla of the kidney as well as FJHN ( i.e. MCKD) also show faults in the uromodulin gene.

Thus several different genes are involved in what appears to be a disease, or group of diseases with similar clinical characteristics. This diversity of genes leading apparently to a single condition, or syndrome, happens in many other inherited diseases, and is called "genetic heterogeneity". Unfortunately, the genes affected in many UK families remain unknown at the moment, although the search continues.

## How is the kidney damaged in FJHN ?

This remains the final and most difficult question. More importantly, what might we do to stop the damage ? To date all signs point to uric acid as the culprit. The first pointer is that a low $FE_{urate}$ in the urine seems to precede any other manifestation of the condition, and is often present in early childhood or even infancy when nothing else seems wrong. Second, allopurinol (which lowers the plasma concentration of uric acid) seems to be capable of arresting the fall-off in kidney function that occurs slowly in this disease, or preventing it if treatment is started early enough and persisted with (*see Simmonds below*). Whether uromodulin, when involved, helps scar the kidney through its accumulation in the cells of the kidney tubules again is not known.

# DIAGNOSIS OF FJHN IN THE LABORATORY

Lynette Fairbanks

So FJHN is a complex disease with multiple genetic causes, all having much the same clinical presentation - a raised plasma uric acid, often, but not invariably, associated with gout in young men, women, and children (of either sex), coupled with the early onset of severe renal disease.

## A child or adolescent with gout - Is the gout due to FJHN, or to another genetic defect?

Even though gout is rare in children and young people, there are several causes for it at this age, especially if male (see PUMPA booklet *"Caring for Children with Lesch-Nyhan Disease*), and it can be the hallmark of other genetic disorders. Some of these other disorders also present first with kidney disease and/or kidney stones, due to the sheer insolubility of uric acid in urine - especially when the urine acidity is high, i.e. the pH is low and the urine is more acid than alkaline.

Other forms of inherited gout - which we call X-linked gout from their inheritance pattern associated with the X chromosome - result from uncontrolled uric acid synthesis by the body, so that there is *over-production*, and the amount of uric acid excreted in the urine is raised compared with normal as well as the plasma urate being high. In contrast, in FJHN the concentration of urate in the blood is indeed raised, but this results from lower than normal excretion by the kidney. Consequently, the first important criteria for diagnosis of FJHN in the laboratory is that urine uric acid must always be measured as well as plasma uric acid.

## How to measure uric acid accurately in blood and urine?

This is the second problem. Uric acid is extremely insoluble outside the body, and will precipitate from urine on cooling, especially if the urine is acid. Consequently, urines must be examined for crystals, both in the urine, or sometimes sticking to the plastic collection bottle. All collection bottles should first be stood in hot water (56˚C) for 30min and shaken vigorously to ensure solution of the uric acid, and then examined again before recording the volume. Aliquots can then be taken and put in a freezer at -20˚C if immediate measurement is not possible.

Uric acid in both blood and urine is measured by a method using the enzyme uricase. This converts only uric acid and not other similar compounds, so the method is very specific. The amount of urate is measured using its absorption of ultra-violet (UV) light. Urate (like many chemical compounds) has a characteristic absorption spectrum in UV light, so the conversion of urate to a non-UV absorbing compound by uricase can be measured, and is thus a very sensitive method as well as a specific one.

The $FE_{urate}$ has been mentioned above (*see Cameron*) as the crucial measurement. It is obtained by measuring the uric acid in a 24h urine, dividing this by the plasma concentration, then factoring it by parallel measurements of creatinine, which is more or less excreted into the urine by filtration only: the result is expressed as a percentage (%) The $FE_{urate}$ varies with age and gender in normal subjects, but is universally low in FJHN. The importance and usefulness of the $FE_{urate}$ is that, unlike both plasma urate concentration and 24 hour urate excretion, it is independent of the intake of purine-rich food in the diet, since urine urate is divided by plasma urate to obtain the result.

## What figures do we get in normal people and those with FJHN ?

The values of urate excretion in the urine from normal people vary greatly, depending mainly on the usual local diet; they are much higher in France, the USA and Australasia than in the UK. Thus normal ranges must be developed by measuring uric acid (UA) in blood and urine of healthy individuals in each country.

The values given below were produced by measuring uric acid (UA) in blood and urine of healthy individuals in the UK eating a normal British diet (which is generally low in purines - i.e. one meat meal per day, and no offal).

| | | | | | | $FE_{urate}$ | |
|---|---|---|---|---|---|---|---|
| | Plasma UA (µmol/l) | | Urine UA (µmol/24h) | | | Normal | FJHN |
| adults >17yrs | (f) | 222 ± 42 | (f) | 2.7 ± 0.5 | (f) | 12.8 ± 2.9 | 5.1 ± 1.5 |
| | (m) | 261 ± 41 | (m) | 3.0 ± 0.5 | (m) | 8.1 ± 3.2 | 5.1 ± 1.6 |
| children <17yrs | (m,f) | 154 ± 41 | (m,f) | 1.36 ± 0.6 | (m,f) | 18.4 ± 5.1 | 5.0 ± 0.5 |

m = male f = female

It can be seen immediately that plasma urate concentrations are lower in women than in men, and even lower in children. This is reflected in the figures for FEurate, which are lowest in men, higher in women and highest of all in children. Generally, affected family members with FJHN show an $FE_{urate}$ below 6.5%.

# PROBLEMS OF DIAGNOSIS IN CHILDREN OF FJHN FAMILIES

Susan PA Rigden

## Screening in apparently normal children

The first important question is: "Can anything be done to prevent a child developing FJHN if he or she has inherited the defective gene from a parent"? The answer is "Yes"! We have shown in a large number of families followed for up to 35 years, that early treatment with allopurinol ameliorates the long-term progression of the renal disease (*see Simmonds below for detail*) . The golden rule, as already stressed, is that when identified they must take their allopurinol every day.

However, the first priority is to identify which children in any family with FJHN have inherited the damaged (mutated) gene for this dominantly-inherited condition. As mentioned already, each child with an affected parent has a 1 in 2 chance of inheriting it. Up until very recently, answering this question has meant metabolic testing of all children born to an affected parents - male or female, as outlined by Dr Fairbanks.

Today we have two options, both of which have drawbacks. They are:

a) Metabolic screening (*see Dr Fairbanks above*)

b) Genetic screening (*see Dr Marinaki below*)

The problems with metabolic screening are:

- sticking to a low purine diet during testing (see p 35-36)
- a 24 hour urine collection into the bottle, with thymol in it to prevent it going "off", requires continence and cooperation
- the blood sample requires a needle stick
- interpretation of results is based on comparison with healthy controls: thus:

| | *Healthy controls* | *FJHN* |
|---|---|---|
| | Normal kidney function | |
| Number of children | 20 | 20 |
| Mean age (range) | 9.1yrs (4-16) | 10.0yrs (4-15) |
| Plasma creatinine (μmol/l) | 57.5 ± 12.2 | 65.7 ± 20.4 |
| Plasma urate (μmol/l) | 192.2 ± 33.6 | 334.7 ± 61.1 |
| FEurate (%) | average 13.2 ± 3.5 | 5.9 ± 1.5 |
| | range (8.7-22.4) | range (3.1 - 8.3) |

The problems with pre-symptomatic genetic testing are:

- the blood sample requires a needle stick
- knowledge of the precise genetic mutation in the child's family is essential
- as yet, not many UK families have an identified genetic mutation.

However, these problems are being, and will be, overcome. To date the metabolic test has helped a number of children from many families and so far one incorrect metabolic diagnosis has been found by genetic testing. The parents were delighted to learn that their child had not inherited FJHN and that the daily allopurinol tablet was no longer necessary.

# THE MOLECULAR DIAGNOSIS OF FJHN

Tony Marinaki

## What is the gene defect FJHN?

The finding that the low excretion of urate in FJHN is present in affected family members from childhood, before any other changes appear, suggests that a defect in the transport of urate in the renal tubule is the major factor in the condition. The efficacy of benzbromarone in FJHN, which inhibits uric acid reabsorption in the proximal tubule, also implicates uric acid in somehow causing the renal lesion.

But what gene or genes are involved in producing this low urate excretion? One major gene is now known, which accounts for one third to a half of the affected families reported in the USA and Europe classified as either **FJHN**, or the closely-related autosomal dominant medullary cystic kidney disease type 2 **(MCKD2)** discussed above. Studies in these families have identified the affected gene as lying on the short arm of chromosome no. 16. The gene codes for a protein produced in the kidney and excreted in the urine, now called "UROMODULIN", but named originally (after its discoverers) Tamm-Horsfall protein. Uromodulin has been a recognized urinary protein for 50 years, but its function was unknown previously. It is made and secreted only towards the end of the first part of the kidney tubule:

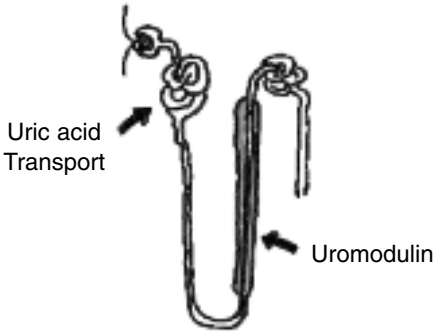



*Figure 4. This diagram shows a single kidney unit, a nephron. The uromodulin is produced in the second, upward half of the loop which each nephron makes down into the interior of the kidney. Most transport of uric acid occurs in the first part of the tubule (arrow on left) away from this site, but some may occur also in the loop.*

In FJHN patients with mutations in the uromodulin gene, uromodulin accumulates within the cells and clogs them up. Although the general opinion is that urate transport into and out of the tubule occurs only in its first (proximal) part, in addition transport in the distal section has been suggested in the past. What role uromodulin might play in determining urate excretion is not known.

## FJHN results from more than one gene defect.

Unlike most inherited disorders, FJHN does not have a basis in a single altered gene. Mutated DNA on at least 3 different chromosomes has been implicated in kindreds from the United Kingdom. So far, linkage to the locus on Chromosome 16 mentioned above (which may be identical to that for MCKD2) has been confirmed in only 5 of the 17 families examined for the uromodulin mutation. A mutated gene has been found also on chromosome 17 (in the gene coding for Hepatocyte nuclear factor 1 beta) in a single family, and there is linkage to an unknown gene on chromosome 1 in another. Since the other British families have none of these defects, there must be yet more genes involved. Whether FJHN in the other, as yet uncharacterized, kindreds results from an isolated defect in a urate transporter, or a regulatory gene, must await identification of the defective genes in all the families.

## The genetics of FJHN

The disorder has an *autosomal dominant* mode of inheritance, irrespective of the underlying genetic defect (see Figure 2 above). This means that the inheritance of the defective gene from a single parent, which is not on the female (X) chromosome, is sufficient to cause the disease. Thus males and females are equally affected in consecutive generations (Fig 2). This is the usual situation, but there is also a possibility that in some families the disorder results from a new mutation, without any previous member being affected. Consequently, in these families there will be no family history of hyperuricaemia and renal failure. Also, penetrance (expression) of the disease may vary in strength. This means that the disorder can apparently "skip" a generation - a parent who should be affected is apparently normal, yet has an affected child.

Moreover, the age of onset of symptoms may vary within a family and also between families. Variable penetrance and onset makes biochemical diagnosis of the disorder difficult, and normal biochemical tests on blood and urine for FJHN during childhood or adolescence does not preclude the possibility that the disorder will manifest later in life. Genetic testing for the defect thus offers certainty to the diagnostic odyssey and offers diagnosis before any symptoms are evident, which is important so that allopurinol therapy can be initiated to help ameliorate the progression of the renal disease.

To date, mutations found in the uromodulin gene detected by DNA sequencing have

clustered in one part of the gene called exons 4 and 5, and preferentially affects parts of the protein chain involving the amino-acid cysteine. Once the mutation has been defined, it is relatively simple to screen family members for the mutation. Further follow-up should be made in consultation with Genetic Services.

# RENAL CYSTS, DIABETES, RAISED URIC ACID AND GOUT CAN ALSO SIGNAL AN UNUSUAL VARIANT OF FJHN

Coralie Bingham

## FJHN has many faces!

FJHN is clearly a complex disease with multiple genetic origins, but all having much the same clinical presentation - raised plasma uric acid, associated with gout in young men, women, and children, coupled with the early onset of severe renal disease if unrecognized and untreated.

## Renal cysts an unusual occurrence in an FJHN variant

Cysts in the kidney are not a feature of FJHN itself, but have been found in a rare kindred who unusually for FJHN, do have such cysts in the kidney - and also early onset of diabetes mellitus. All the affected family members have hyperuricaemia, which has caused gout in several. This kindred has been demonstrated to have a defect in a particular gene called *HNF-1ß (hepatocyte nuclear factor 1ß).* Mutations in the HNF-1ß gene cause the "renal cysts and diabetes" (RCAD) syndrome. The cardinal features of this are disorders of renal development, in particular renal cysts, and early onset diabetes. Hyperuricaemia and gout are also features of this condition.

## Altered uric acid transport in the kidney may be the cause

The hyperuricaemia is likely to be due to altered uric acid transport in the kidney. The HNF-1ß gene is expressed in the first (proximal) part of the kidney tubules from the earliest phases of development of the kidney. It has been speculated that reduced HNF-1ß activity reduces transcription (reading and expression) of the human urate transporter, mediated through binding sites for HNF-1ß in the transporter gene.

## Allopurinol may help prevent renal disease progression

The important point in terms of prognosis for kindreds with this combination is that, as with all the other UK FJHN kindreds identified sufficiently early (ie before the onset

of severe renal disease), allopurinol has not only prevented the progression of the renal lesion, but the 3 children in the family found with an HNF-1ß mutation showed an improvement in renal function whilst on treatment.

## Comment

Screening for HNF-1ß mutations in FJHN is particularly appropriate in those unusual families with renal cysts, or other abnormalities of renal development, or where there is a history of diabetes as well as hyperuricaemia and early-onset gout in young members of the family, both men women and children.

# WHY DO WE USE ALLOPURINOL TO TREAT FJHN?

H Anne Simmonds

## First, what is allopurinol?

Allopurinol is a synthetic chemical medicine, with a structure similar to that of the purine in the PUMPA logo on the cover of this booklet, but slightly altered. Allopurinol was first developed in the 1960s, not to treat gout but to treat cancerous tumours, but was abandoned for this purpose because it did not work. Coincidentally, it was noted to lower uric acid concentrations in the blood, and has been used to treat gout since that time.

## What does allopurinol do?

It binds to and inhibits the enzyme xanthine oxidoreductase (XOR), which normally converts the precursor purine (called xanthine) into uric acid within the body. Thus allopurinol diminishes uric acid production, and hence the concentration in the blood, and in turn the amount filtered by the kidney and available for reabsorption in the tubule. The handling of urate in the kidney tubule is complicated, going both ways, into and out of the cells lining the tubule as mentioned above. It is not clear whether in FJHN more uric acid than normal is reabsorbed into the cells lining the tubules from the lumen, or less is excreted back from the tubular cells either into the tubular lumen, or into the blood. However by lowering the uric acid in both the urine and the tubular cells, allopurinol reduces the possibility of (further) kidney damage by uric acid.

## Is early allopurinol treatment important?

Yes. Irrespective of the exact genetic basis, very early recognition of FJHN and treatment with allopurinol reduces the rapid decline of kidney function seen earlier in untreated patients. In such families, all members recognised as having FJHN and treated sufficiently early - and who were compliant with treatment - have survived.

Many such families had a history of 'familial renal disease - cause unknown' which led to early death in previous generations. These families also underline the importance of measuring uric acid in blood and urine of all family members because (as one would expect for a dominantly-inherited disorder), 50% of other family members, some of whom have no symptoms at all, are also found to have raised plasma uric acid allowing for age and gender. All will need treatment with allopurinol.

The importance of treating all affected family members is illustrated by our first family, recognized in 1974. An Austrian mother who had developed gout aged 29 died of kidney disease whilst needing dialysis treatment, at the age of only 36. Her siblings could not be traced, until an article in a medical journal in 1998 described another Austrian woman with severe renal disease, who had developed gout as a girl, and whose son also had renal disease, and who were members of the same family (see Figure 2 above). Allopurinol, plus benzbromarone (see next section) has halted further kidney function decline in both. Had family contact been maintained, they could have been recognized and treated earlier.

## Teenagers must be persuaded to take their allopurinol!

In some cases attention was first drawn to a family by a child presenting with actual gout - the youngest of these being the girl of 9, the twin sister mentioned earlier in this booklet by Lesley Kinge. Both girls were poorly compliant with treatment during their teens and Lesley describes the consequences, illustrated in Figure 5 (K2 IV3, patient indicated by open circles) - which also brings up the importance of control of high blood pressure and

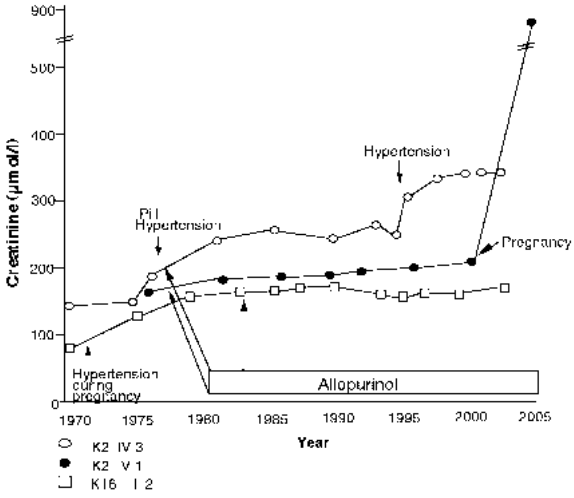



*Figure 5. This shows the progress of three women under allopurinol treatment for up to 35 years, indicated by their kidney function (plasma creatinine concentrations). It shows also the rapid deterioration of one patient following pregnancy, whose renal function had been relatively stable over 25 years taking allopurinol.*

avoidance of oral contraceptives. Other families with good compliance to the treatment regimen and normal renal function when first starting allopurinol, have retained normal renal function. It is important also that those like her cousin (K2 V1, closed circles in diagram below) already with signs of even early kidney damage at diagnosis (for example a plasma creatinine concentration greater than normal but less than 200 μmol/l) have shown only a slow decline with time. Sadly, all those patients who for whatever reason were never treated have progressed over only a few years to end-stage renal disease and have died, required dialysis, or had to have a kidney transplant.

Thus two key messages emerge:

1. For all patients of either sex, allopurinol is effective but compliance is vital, as is control of blood pressure
2. For any woman thinking of becoming pregnant, the main question is whether kidney function is normal. If this is below about 70 /ml/min, there is a real risk of accelerating any decline in kidney function. The lower the kidney function, the greater the risk (*see Cameron below*).

Most patients take allopurinol without any problems even for many years - although problems, principally rashes, may arise if the dose is not reduced appropriately in those with reduced kidney function. A few patients cannot take it all because of allergy (*see Vanhinsburgh below*). In that case it may be possible to de-sensitise them with a graduated series of injections of the drug starting with minute doses, or to use other agents to lower the uric acid (*see Goldsmith next section, and Vanhinsburgh*).

# ALTERNATIVES TO ALLOPURINOL, AND BLOOD PRESSURE CONTROL

David Goldsmith

Patients with FJHN are much more prone to gout than the general run of patients with kidney disease. Indeed as we have seen this is sometimes the way the families are first diagnosed. The importance of FJHN patients taking their allopurinol to lower their uric acid has been underlined. Why is this so vital? Simply because FJHN patients differ from the classic gout affecting overweight middle-aged men (the most common form of gout) in several ways.

First today in the usual gouty middle-aged male kidney disease is rare, while it is inevitable in FJHN, but can be prevented - or halted - by lowering the blood uric acid. Second FJHN patients are young, slender, both female and male - sometimes children in whom gout is even more unusual.

In patients with other causes for their renal failure gout is rare also, but may be associated with chronic renal failure when high blood pressure (BP) develops. However by the time dialysis is needed gout is uncommon, as dialysis clears out some of the plasma urate .

For some few gouty patients (either classic gout, or FJHN) allopurinol can be associated with severe allergic reactions, as experienced by a 14 year-old girl with FJHN (see Vanhinsburgh below). Fortunately, although rare, there is an alternative treatment - **benzbromarone** (Figure 6). This medicine belongs to a family of drugs called uricosuric agents - that is, they lower the blood uric acid concentration by **increasing uric acid excretion** through the kidney. This is contrast to allopurinol, which as we have seen above **blocks uric acid formation in the body.** Uricosuric agents (such as probenecid, which is still used today although rather rarely) were the main treatment for classic gout in the last century before allopurinol was introduced in the 1960s. However, benzbromarone is ten times more effective as a uricosuric agent than probenecid, works even in the presence of considerable degree of kidney failure as probenecid does not, and is an important alternative to allopurinol.

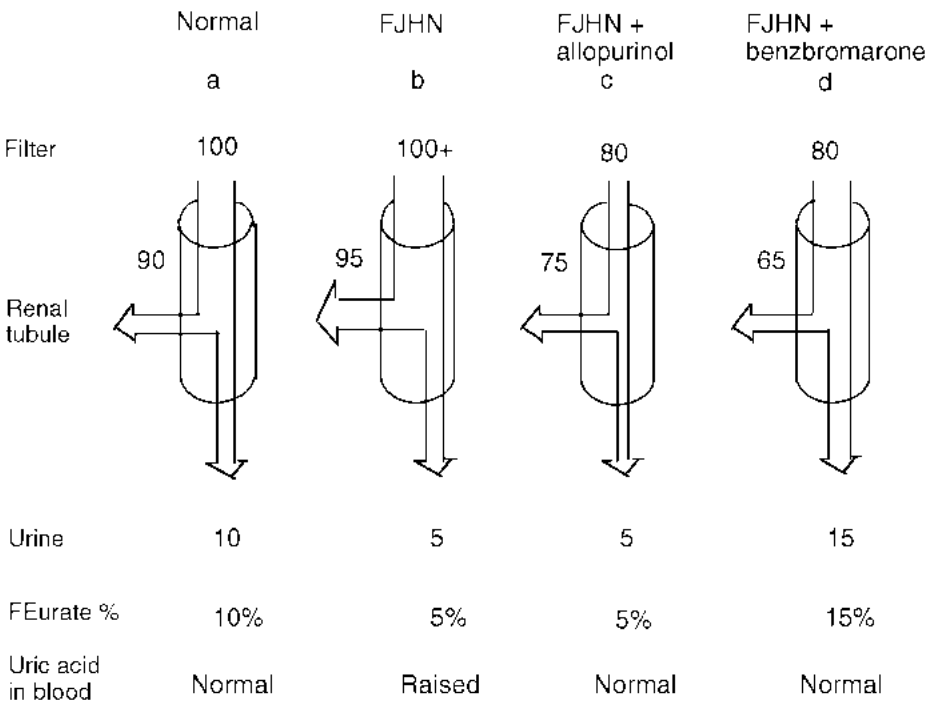
Some doctors suggest that the use of allopurinol plus benzbromarone may be the best treatment for FJHN, as in the Austrian family discussed by Dr Simmonds above. This combination has proved effective in some patients already suffering some degree of

renal impairment when first diagnosed, when lowering the uric acid with allopurinol alone has often proved difficult. One problem with benzbromarone is that it is difficult to obtain, as it has never been licensed in Britain. This is in part because (very rarely) it can cause liver failure. Today it must be obtained from Germany or South Africa.

The reason gout may develop when blood pressure rises is that hypertension reduces uric acid excretion by the kidney, and also treatment with the blood-pressure lowering medicines commonly used (such as the diuretics bendrofluazide and furosemide), will reduce uric acid excretion even further. This effect of furosemide is illustrated best in women after the menopause who have normal renal function (and in whom gout is normally rare), who may develop acute gout following the start of treatment for raised blood pressure.

Fortunately, other blood pressure lowering medicines (belonging to the angiotensin-antagonist class) can be used which do not enhance uric acid reabsorption. Losartan is one such effective blood-pressure lowering medicine with the additional beneficial "side-effect" of actually reducing plasma uric acid levels 10 - 15% as well. It is also proven to reduce the incidence and progression of diabetic damage to the kidney, and is thus a logical and well-tolerated choice for raised blood pressure in anyone with high blood pressure, kidney disease with proteinuria, FJHN or the classic type of gout.

*Figure 6. The handling of urate in the kidney tubules in health and in FJHN (left) , and the effect on this of the drugs used to treat it (right)* (discussed in Simmonds and Goldsmith above)




a) Normally of every 100 units of uric acid filtered 90 units are rebsorbed and 10 excreted

b) In FJHN 95 units are reabsorbed and only 5 excreted, so the uric acid in the blood rises

c) In FJHN on allopurinol blood uric acid is rediuced, but the amount excreted does not change

d) In FJHN on benzbromarone blood uric acid is reduced because less uric acid is reabsorbed

# FJHN IN WOMEN AND GIRLS - A SPECIAL PROBLEM

J Stewart Cameron

Gout has traditionally been considered as a disease of middle-aged or older men, and indeed this has always been so. It is true as well however that over the past 25 years or so gout has become more common in older women, often beginning with deposits of uric acid in the fingers or elsewhere rather than with an acute, hot painful joint. This increase relates in the main to widespread use in this group of people of medicines which reduce the excretion of uric acid - particularly diuretics such as bendrofluazide and furosemide for heart problems and/or high blood pressure (*see Goldsmith above*).

The main reason that women are normally protected from getting gout is that the fractional excretion of urate filtered in the kidney ($FE_{urate}$ - *see Cameron, and Fairbanks above*) is high in children before puberty, and in women, which means that however large their intake of purine-rich food, the concentration of uric acid in the blood remains reasonable. As the likelihood of clinical gout increases steadily with higher blood uric acid levels, gout hardly ever appears in young women as normally they have low blood urate concentrations.

However girls and women with FJHN have a very low $FE_{urate}$ just as men with the condition do- about 3-5% (see Fairbanks above). Thus they are no longer protected from getting gout. This can happen when they are fertile, and wishing either to use contraceptives and/or become pregnant. These circumstances present them and their medical attendants with several problems which do not normally arise in middle-aged male gouty patients!

## Contraception

Apart from trying to persuade reluctant teenagers to take their allopurinol (a point emphasized throughout this booklet), they will need to modify their approach to contraception. Certainly if they have any degree of kidney damage already, however mild, they should not use oestrogen-containing contraceptives. The reason for this is that such medicines tend to raise the blood pressure, and a vicious circle of rising blood pressure and increasing kidney damage can - and does - occur. If kidney function is normal (and this means careful assessment, not just an

apparently normal plasma creatinine concentration), it is still probably best to avoid oestrogen-containing contraceptives for this reason. Barrier methods should be used, such as condoms.

## Pregnancy

Young women with FJHN who wish to become pregnant face several problems.

First, if their kidney function is anything less than normal, they face the possibility that pregnancy will accelerate the decline in their kidney function, most usually immediately after the pregnancy. This was illustrated in the diagram in Simmonds' article above (Figure 5). This danger is faced by people with kidney failure of mild degree from any cause, and is not special to FJHN. It is associated also with a tendency for the blood pressure to rise in the latter part of pregnancy, and not to return to normal afterwards. Only the individual herself can assess whether she and her partner are willing to take this risk in order to start or expand a family. Patients with obvious kidney damage (say a creatinine clearance less than 70 ml/min or plama creatinine of 150μmol/l or more) probably should forego pregnancy, as the chance of further kidney damage becomes overwhelming; but again this must be an individual's decision. One must also take into account that pregnancy is possible after successful kidney transplantation, if there is enough time to carry this through and get settled before the menopause sets in.

Moreover today several techniques of artificial or aided conception are, or are becoming available. First, eggs can be obtained, frozen and fertilised later for implantation in the womb - controversially even if the mother is past the menopause; or even a surrogate mother can be involved if kidney function is insufficient to carry the pregnancy safely. If the family has a recognized mutation such as one in the uromodulin gene on chromosome 16, it is becoming possible to see whether or not the embryo has the mutation before implantation, and thus which embryo to use, although this has not been done yet in practice in FJHN. Obviously, all this raises complex ethical issues.

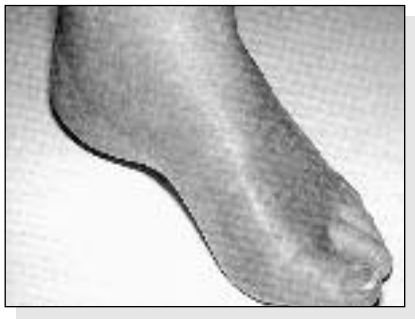
The second problem concerns medicines. Allopurinol has never properly been tested through pregnancy to see if it damages the fetus early on, although we know of two women who did use it through pregnancy without problems, and there may be other similar cases. The worry arises because the chemical structure of allopurinol suggests that it might cause problems for the fetus, but other related medicines have rather

surprisingly turned out to be safe in this respect (for example the transplant drug azathioprine). On balance it is probably better to avoid allopurinol, remembering that by the time a woman knows she is pregnant, the time of maximum danger for the fetus from drugs is already past. Thus allopurinol should be stopped *first* before trying to become pregnant, and only re-started after completion of the pregnancy. Allopurinol is present also in milk, but can probably be begun safely during breast-feeding as it is not toxic to a developed baby any more than to an adult. Fortunately, the excretion of uric acid normally increases during pregnancy, along with a temporary increase in overall kidney function, so attacks of actual gout are very unlikely.

Benzbromarone (*see Goldsmith above*) seems a possible substitute for allopurinol, but again has never been evaluated during pregnancy, so we simply so not know if it is safe and it is better avoided. However the other drug which increases $FE_{urate}$, probenecid (Benemid) although weaker in its action, has been extensively used during pregnancy for purposes other than its effects on uric acid, and been found to be safe for the fetus. It is also more easily available in the UK at the moment. Therefore, if any drug is to be taken during pregnancy to prevent gout, this should be it. Should a rare acute attack of gout occur during pregnancy, again the medicines which can be used are limited. Probably the best approach is to put a needle into the joint, draw off fluid (which relieves the pain a lot anyway) and inject corticosteroids, rather than using anti-gout medicines by mouth. Of these colchicine - which is often used for acute gout - is probably safe after the first three months, and better than non-steroidal anti-inflammatory drugs (such as naproxen and indomethacin) which can affect the baby even late in pregnancy and after the delivery.

# ATTACKS OF ACUTE GOUT

J Stewart Cameron



By the time most patients with FJHN know they have it, they are already on some treatment which usually prevents acute attacks of gout. Also many patients with FJHN never experience acute attacks at all. However especially to begin with, attacks may be troublesome, and if treatment is discontinued they can pop up at any time!

Most people rate the pain of an acute attack of gout as one of the most painful events in their lives. Doctors also agree that perhaps only the pain of passing kidney stones is worse.

Attacks of gout usually affect joints in the periphery - that is hands and feet particularly. One explanation that had been advanced for this for this is that these parts are cooler than the rest of the body, and the uric acid is less soluble in cooler tissue fluids. The big toe (pictured above) seems very vulnerable.

## Treatment

How can acute gout be treated? First, rest is most important - moving or jogging the swollen joint can be agonizingly painful. Packing it in ice is effective also - a bag of frozen peas is a good way to do this as it can be modelled to the contours of the part, but the hand or foot must be protected from frost burn/bite by exposing it at intervals. Analgesics will help dull the pain - paracetamol is usually not strong enough, and some stronger painkiller will often be needed.

The main problem in acute gout is inflammation, triggered by the uric acid crystals, so usually medicines to counteract this will be given as soon as possible. An old fashioned but very effective "natural" remedy is colchicine from the autumn crocus plant, which has been used for 2000 years. Its main problem is that although effective, it is toxic and in effective doses usually cases diarrhoea. It also takes a day or more to work effectively. Thus today, many doctors use NSAID drugs instead, of which the prototype is indomethacin (Indocid), although diclofenac (Voltarol,

Diclomax) and naproxen (Naprosyn) are sometimes used. Ibuprofen (Brufen) is generally not strong enough to quell an attack of acute gout. Newer, more specific anti-inflammatory agents are available such as etoricoxib (Arcoxia) which has been shown to be equally as effective as colchicine. Steroids such as prednisolone, both by mouth and injected into the joint are very effective also. None of these medicines need be taken for very long - usually only a week or two at the most, and then long-term treatment can be begun, usually with allopurinol. Sometimes this starts off further acute attacks, for reasons which are not entirely clear, and it may be worth taking a small doses of colchicine as well for three or six months after starting the allopurinol.

# TREATING ESTABLISHED KIDNEY FAILURE IN FJHN

G Venkat Raman & J Stewart Cameron

Those unlucky enough to develop kidney failure from FJHN need treatment which does not differ in principle or detail from that for kidney failure from any commoner cause. As most families affected by FJHN know, two main treatments are available: dialysis, and kidney transplantation. The details of these treatments need not be given here, but are readily available from the contacts given at the end of the booklet.

Kidney transplantation is generally regarded as giving a better quality and duration of life than dialysis, but in practice is limited by the need for a kidney donor. This can be a blood relative, or someone unrelated with a strong emotional relationship. Obviously members of the family who themselves have FJHN cannot give a kidney, as the condition arises from a kidney defect (*see Cameron above*).

Ironically for people with FJHN, recipients of kidney transplants (which should cure the FJHN) may actually suffer from gout. This is not from recurrence of their original disease but can happen to any transplant recipient, whatever the cause of their kidney failure. It arises partly from poor function in the transplanted kidney, but is mostly the result of side-effects of medicines, especially ciclosporin and diuretic drugs (*see Goldsmith*). Fortunately, alternative regimes that do not induce gout to nearly the same extent are now available.

If gout should appear, patients with a transplant face special problems with regard to their medicines which need careful discussion with their doctors. If allopurinol is used to prevent gout, the dose of the anti-rejection drug azathioprine should be reduced to about 25 mg daily from the usual 100-150 mg. This arises because azathioprine is broken down by the same enzyme which gives rise to uric acid and is inhibited by allopurinol. Then potentially toxic levels of the active form of azathioprine accumulate in the blood. Some physicians prefer to avoid azathioprine altogether for patients who need allopurinol. If ciclosporin is thought to be the main culprit in causing the gout its dose can be reduced or stopped altogether. Diuretics should be avoided.

For an attack of acute gout one of the group of anti-inflammatory drugs called NSAIDs, such as indomethacin or diclofenac are often used (*see Cameron, acute gout, above*). However these reduce the blood supply the transplanted kidney, and it is better to use injection of steroids into the affected joint(s), and/or a temporary increase of the dose of steroids by mouth to relieve the pain. Colchicine can be used also but often causes diarrhoea and is slow to bring relief.

# ALLOPURINOL ALLERGY AND ALTERNATIVE TREATMENT: A PATIENT'S VIEW

Lisa Vanhinsburgh

## Gout at only 14!

*Lisa and her son Ryan, who both have FJHN*

I was diagnosed with gout as a teenager and told it was very rare in someone my age - especially if female. I was given indomethecin (*an anti-inflammatory NSAID medicine - editor*) and advised to take it when the gout flared up, which was very frequent. The attacks continued over the years. Consequently, when I got married and wished to have children we sought professional advice because I was uncertain about the affect of gout on the baby. The consultant told us that sometimes gout could affect the kidneys and had tests done which showed I had only 70% of normal renal function.

## Laboratory tests confirm FJHN

The Purine Research Unit at Guy's Hospital was contacted and did more tests which revealed I had a rare medical condition called familial juvenile gout, abbreviated FJHN. Basically a gene in the kidney that normally controls the level of uric acid in the body was faulty so over the years uric acid had built up causing gout and had started to destroy my kidneys. I was recommended to take allopurinol.

## Allergy to allopurinol can be excruciatingly painful

I took half a tablet, but within a few hours my face started to itch and swell up. Both my lips and eyes became puffy, I had hallucinations and was very sick. Over a period of hours my skin started to tingle all over. At first it just felt strange, but got stronger and more painful, like having lots of pins pushed into my skin. I later learnt that this

was the nerve endings being affected by the allergy. This continued for a few days and ended with every part of my body being covered in eczema. It started at my head and worked its way down my body. In all I was ill for 2-3 weeks

## Benzbromarone is an acceptable alternative

Obviously allopurinol was unacceptable and benzbromarone (a drug unlicensed in Britain, but widely used until recently in Europe) was suggested. Since its use in pregnancy was unknown (*see Cameron above*), I had no treatment until my son was born. Pregnancy was uneventful apart from high blood pressure and my son was born 5 weeks early by emergency caesarian, thankfully healthy. However my kidney function had fallen to 50% so I started benzbromarone again and everything was OK until it was stopped due to an abnormal heart beat. When it was finally found this had nothing to do with benzbromarone it was recommenced, but during this time my kidney function had fallen to 30%. Happily, back again on benzbromarone it seems to have stabilized at this level.

## Children must be screened and treated too

As soon as I was told FJHN was hereditary, I had my son tested when old enough to collect samples for the metabolic test. At the age of 7 it was found he too had the disorder. Because of my reaction he was desensitized to allopurinol in hospital and now takes his allopurinol daily.

Although we both face a life-time of drug taking, I can't thank the Purine Research Unit and medical staff at Guy's Hospital enough. Without their hard work my son's future would not look very bright - and I might not even be here!

# INSTRUCTIONS FOR A LOW PURINE/CAFFEINE FREE DIET

The instructions below apply to the collection of samples for purine investigations, but it may be helpful to parents to know which foods are rich in purines and thus should be avoided when preparing meals.

For purine studies it is advisable to try to eat a diet identical with your normal diet in terms of butter, fats, bread potatoes and other vegetables etc, but avoid the meat, fish and other food and drink outlined below with a high purine content in Section 1, and substitute a low purine equivalent from section 2 and 3.

## 1. Food and beverages not allowed

1.1 OFFAL - sweetbreads, heart, liver, kidney, and pate.

1.2 SEAFOOD - Sardines, sprats, herring, bloaters, fish roe, trout or salmon. Lobster, crab, prawns, oysters, cockles, mussels etc.

1.3. VEGETABLES - Asparagus, avocado pears, peas, spinach, mushrooms, broad beans, cauliflower.

1.4 Soya products, pulses and legumes.

1.5 Alcoholic beverages (beer) and yeast extracts. Meat or vegetable extracts (Marmite, Vegemite, Bovril etc).

1.6 Tea, coffee (other than decaffeinated); cocoa products such as Ovaltine, chocolate or chocolate biscuits, chocolate puddings; and Coca-Cola, Pepsi-Cola, or Lucozade.

(NB 1.6 only refers to diet when samples are being collected for the laboratory. These foods and beverages all contain methylated xanthines, which make analysis difficult in the laboratory)

## 2. Foods and beverages allowed

2.1 Milk, cheese, eggs, butter, margarine, cream, ice cream

2.2 Bread, flour, cakes, scones, biscuits, cereals.

2.3 Sugar, jam, marmalade, honey and sweets.

2.4 Lettuce and tomato (e.g.: salads).

2.5 Fresh, cooked or tinned fruits, nuts.

2.6 Puddings (milk etc), except those containing chocolate/cocoa.

2.7 Decaffeinated coffee or tea.

2.8 Fruit juices, soft drinks EXCEPT Coca-Cola etc.

## 3. Foods allowed in moderation (one meal per day)

3.1 Beef, lamb or mutton, port, bacon, ham, poultry, sausages, tongue, and meat soups.

3.2 Small helpings of vegetables (except those in 1) carrots, potatoes, leeks, cabbage, brussel sprouts, runner and French beans, marrow, courgettes.

3.3 Fish (except those in 1).

# SUGGESTIONS FOR FURTHER READING

Cameron JS, Simmonds HA. Hereditary hyperuricemia and renal disease. *Seminars in Nephrology* 2005, volume 20, pages 9-18. WB Saunders, Philadelphia

Marinaki AM, Cameron JS, Simmonds JS. Inherited disorders of purine metabolism and transport. In: *Oxford textbook of clinical nephrology 3rd edition.* Eds Davison A, Cameron JS, Grünfeld JP et al. Oxford University Press, Oxford, 2005. (Vol 3) Pp 2381-2395.

Fairbanks L, Cameron JS, Venkat Raman G et al. Early treatment with allopurinol in familial juvenile hyperuricaemic nephropathy (FJHN) ameliorates the long-term progression of the renal disease. *Quarterly Journal of Medicine* 2002, volume 95, pages 597-607. Oxford University Press, Oxford.

- these three articles in turn contain details of a large number of other papers, and chapters in books, on the subject of FJHN. They are aimed predominantly at physicians and other health professionals.

A book for patients about gout in general contains much information about gout and the medicines used to treat it, and purines. Although it mentions FJHN and discusses it briefly, it deals mainly with middle-aged male gout

Grahame R, Simmonds HA, Carrey E. At your fingertips: Gout. Class Publishing, Barb House, London 2003. ISBN 1 85959 067 5.

# CONTACT ADDRESSES FOR FURTHER HELP

## Information and support:

Mrs Joan Martin, patient support group, PUMPA, Southlands, Keymer Road, Burgess Hill, West Sussex RH15 OAN tel: 01444 248 581.

Dr. Anne Simmonds or Dr Lynette Fairbanks, Purine Research Laboratory, 5th Floor Thmas Guy House, Guy's Hospital, London Bridge SE1 9RT tel: 0207 188 1276, fax: 0207 188 1280. E-mail: anne.simmonds@kcl.ac.uk.

## For information about attacks of gout :

UK Gout Society. PO Box 527 London WC1V 7YP. E-mail: info@ukgoutsociety.org website: www.ukgoutsociety.org

(this deals almost entirely with gout in the middle-aged, and does not contain information specifically on FJHN. However it has some useful general tips, and also a chat forum and questions & answers facility)

For further information about the RCAD syndrome or the HNF-1B gene contact: Dr Coralie Bingham ( e-mail: C.Bingham@exeter.ac.uk)

Information and support (including financial grants, or grants in kind to patients with kidney diseases and their families):

NKRF. National Kidney Research Fund, King's Chambers, Priestgate, Peterborough PE1 1FG. www.nkrf.org.uk.

Helpline: 0845 300 1499 OR text to 07786 200 505. OR helpline@nkrf.org.uk.

BKPA: British Kidney Patients Association. President: Elizabeth Ward. Address: Bordon Hants. GU35 9JZ. Tel: 01420 472021 Fax: 01420 475831.

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# Introduction

The objective of this book is to provide patients, parents and professionals with the basic facts about Familial Juvenile Hyperuricemic Nephropathy (FJHN) in a simple and understandable fashion - its clinical presentation, biochemistry and progression, and particularly what treatments are available. To this end we have drawn on the experience of those involved at every level in Great Britain.

This book forms part of a series aimed at covering signs, symptoms and treatments for disorders under the PUMPA umbrella, and will fill a much-needed gap. Like the first publication on Lesch-Nyhan Disease, FJHN has been the subject of several annual Seminars at Guy's and this book follows the third Seminar in November 2004, which reported progress in diagnosis using genetic probes, also enabling pre-symptomatic detection of FJHN in some families

The publishers wish to acknowledge the valuable contribution to the booklet from:
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Dr David Goldsmith, Consultant Nephrologist*
Dr Lynette Fairbanks, Principal Biochemist*
Dr Tony Marinaki, Principal Biochemist *
Dr Anne Simmonds Emeritus Senior Lecturer*
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