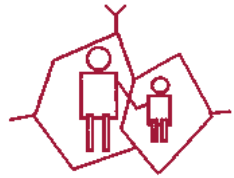

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Caring for Children with

ADENINE PHOSPHORIBOSYL TRANSFERASE (APRT) DEFICIENCY

PUMPA

A Guide for Patients, Parents and Professionals

Introduction

The objective of this booklet is to provide patients, parents and professionals with the basic facts about the purine disorder, adenine phosphoribosyltransferase (APRT) deficiency, 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 worldwide. Clinically APRT deficiency presents as urolithiasis - which in layman's language means stones in the kidney, or urinary tract. Importantly, APRT is one of the few treatable disorders under the PUMPA umbrella, but it MUST be recognized and treated early.

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 (LND), and the second on familial juvenile gout (FJHN), APRT deficiency has been the subject of annual PUMPA Seminars at Guy's Hospital, London. This booklet summarises the experience of patients and parents, and reports progress in diagnosis, enabling pre-symptomatic detection of APRT deficiency in some families. Although APRT is a rare inborn error of metabolism it can lead to kidney stone formation, chronic renal failure and kidney transplantation. Consequently, it is particularly important that the nephrology community are aware of this disorder as a potential cause of unexplained renal disease.

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Notes

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Living with APRT

A FAMILY HISTORY

Carlos D'hont

I would like to tell our story of the long and difficult way we had to go with our son Bart. I hope that, by doing so, I will be able to illustrate some other aspects of APRT deficiency, which are not less important than the medical aspects.

Bart is our second son and was born in January 1973 in Belgium. He was a normal baby but very quiet. I remember it was very cold when we brought him home from the maternity ward. After 6 weeks we returned with Bart to the former Republic of Zaire, where we had lived and worked for several years. Initially there were no problems with Bart: he grew normally. One day Annie my wife discovered some reddish-brown sand in his nappy. We thought that some construction works going on in the house might be responsible and didn't pay much further attention to it.

This changed when we discovered that the sand appeared in the nappy almost every day. We really started to worry when on top of that Bart started to have high fever. So we went to our company doctor who prescribed an antibiotic. But instead of bringing the temperature down it resulted only in worsening the situation: some days Bart had very high fever and we found more and more of this brown reddish sand in his nappies, the excretion of which was obviously painful (Figure 1).

Our company doctor then decided to send us to Lubumbashi, some 800 km from the small town where we lived, to consult a paediatrician. Bart was examined and a number of tests performed. The sand was thought to be uric acid and bicarbonate was prescribed, together with antibiotics. The paediatrician was honest enough to tell us she had never seen a young child with uric acid stones, but she saw no other solution than the treatment with bicarbonate. So we flew back home not much wiser than before. However, even with treatment the situation did not change much and after

some weeks we decided that Bart would have to return to Belgium where we could find out what was wrong with our son. Back in Belgium Annie and Bart started a long journey that consisted mainly of visits to doctors and hospital admissions for one or more days. It was a nightmare: one day they lost all Barts records and we had to do all the tests over again. On another occasion Annie was accused of putting sand in the nappies, and one doctor went as far as to tell her it was a lost cause and there was no use visiting doctors any more.

In the meantime the symptoms persisted and another worrying fact became obvious, at the age of 16 months, Bart, who was a heavy child then, could still not walk and the doctors told us that Bart had suffered brain damage and that we had to be prepared that he would spend his life in a wheelchair, provided the brain damage was not progressive. This, coupled with the fact that the stones were uric acid led to the suggestion that Bart had Lesch-Nyhan disease. (It transpired later that Bart had a temporary muscle problem unrelated to APRT deficiency. But at that time the deficiency was not known). In the meantime the excretion of small stones continued, mostly with great distress for Bart.

Hopes raised after further tests sent to London and a diagnosis made!

One day we got the name and address of Prof Karel Van Acker and we decided to visit him in Antwerp. I remember very well holding my son in my arms and meeting the Professor in the corridor of the hospital. He immediately took out a tape measure there in the corridor put it around Barts head and later told us after further examination that our son had no brain affection and should be considered normal in this respect, which we could hardly believe anymore. As for the problem of the stones this would be investigated. So again we had to leave our son in the hospital for more blood tests, which like all children and most adults he did not like at all! After some weeks we got news and it was very good news. Through Professor van Acker's contacts with a research team in London, blood, urine and small stones had been investigated and the first ever diagnosis of APRT deficiency was made. The unusual round brown crystals in Bart's urine (See Fairbanks) were not uric acid, but a chemical with a dreadful name called 2,8-dihydroxyadenine - the cause of the stones - which had never been described before.

For us it was as if heaven had come down on earth and we were told we could hope to keep our son!

Later on we met Dr Simmonds and Professor Cameron and realized how fortunate we were, but all our problems were not over however. The main one was treatment. Fortunately the London team had also been working on a (then) new drug for gout called allopurinol (which reduced the uric acid in gout by inhibiting the enzyme xanthine dehydrogenase (XDH), responsible for forming the uric acid. By chance, this same enzyme was also responsible for forming Bart's stones, and after several trials the exact allopurinol dose was found and from then on the problems disappeared.

On another occasion we had to assemble all the available members of both our families for blood tests, which was quite an undertaking. The objective was to find if any, or how many more members of our families carried the defective APRT gene. It appeared from these investigations that the APRT deficiency could be dated back to the early 1800's in Annies family, but I was the only carrier in my family and was what they called a 'new' mutation.

APRT Deficient Kindred

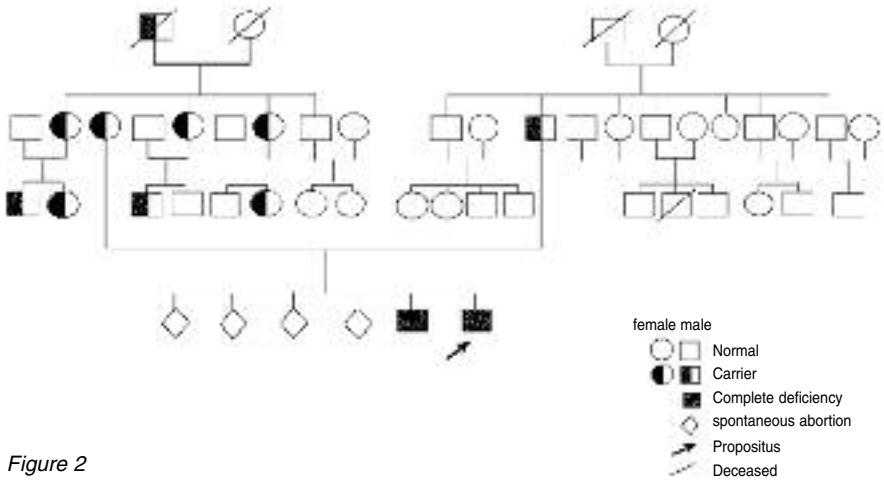


Figure 2

What exactly is APRT Deficiency

Dr Tony Marinaki

What Exactly is APRT?

APRT is the abbreviated name for an uncommon disorder of purine metabolism first described in 1974. The disorder arises from one of a number of alterations (mutations) in the DNA sequence of a particular gene which codes for an enzyme of importance in the recycling of the purine adenine (see Simmonds), resulting in a damaged enzyme which does not work properly.

Why the initials APRT?

The A is for "adenine" an important purine compound found in many molecules throughout the body. The PRT stands for "PhosphoRibosyl Transferase" which describes what happens to the adenine under the influence of the enzyme, so the whole name is Adenine PhosphoRibosyl Transferase, abbreviated to APRT. The defect is inherited in a reproducible fashion, so the condition runs in families. As a result of a lack of APRT adenine accumulates which is itself of no significance. However the excess adenine is converted to 2,8-DiHydroxyAdenine (DHA for short) (see Simmonds), which is very insoluble and the root of the problems in APRT deficiency. This gives rise to brown crystals in the urine (Figure 1), as the DHA is excreted through the kidneys, to the formation of crystals in the kidneys themselves and to actual stones, which may be quite large (see Cameron).

The defective gene for APRT is inherited in what is called a ***recessive*** fashion. DNA is located in chromosomes within the nucleus of cells, and each chromosome has two copies - a pair. The gene for APRT is carried on the long arm of chromosome no. 16, out of the 23 pairs of chromosomes we all have (see Sahota). One of each pair comes from the mother, and one from the father. In the case of APRT deficiency if someone has one chromosome with the defect they will be a carrier, capable of passing the disease, but without any problems themselves. However if two carriers have children, then there is the possibility of some of their children having both copies of the gene with the defect, and thus to get the disease. A moment's calculation shows that the chances of any one child of two carriers being normal or of having the disease are 1:4, whilst their chance of being a carrier like their parents is 1:2 .

APRT passes via both parents to 1 in 4 of their children

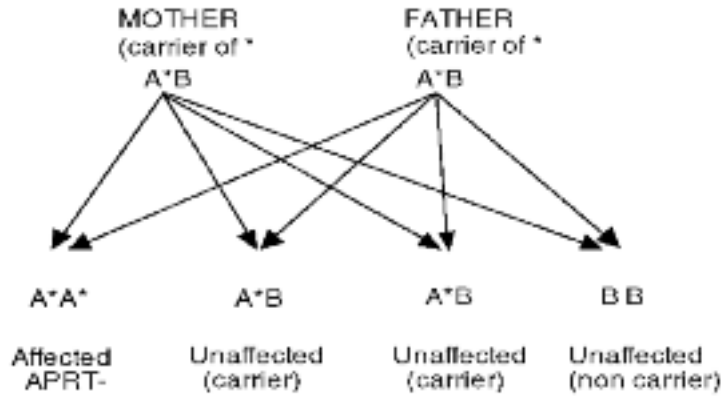


Figure 3

When is a Uric Acid Stone not a Uric Acid Stone?

Dr Anne Simmonds

The answer is when it is composed of an unusual chemical called 2,8-dihydroxyadenine (DHA). DHA is not normally found in our body, but accumulates when APRT is defective. The full name for APRT is a dreadful mouthful and has been explained by Dr Marinaki.

Why did the laboratory in Zaire and Belgium mistake Bart's crystals (Fig 1) and stones below (Figure 4) for uric acid?

First, uric acid is overwhelmingly the most common cause of purine stones.

Second, all of the three types of purine stones formed by humans react in all available chemical tests for uric acid exactly as though they were uric acid, irrespective of whether they are composed of uric acid itself (most common) or rarely, DHA (the subject of this booklet) or xanthine (to be the subject of a later booklet).

All these three stone types like uric acid do not show up on ordinary X-rays, but they all show up as a "starry" picture on ultrasound examination (see Cameron).

We now know from APRT deficient patients identified later in Japanese populations, that the mutation causing APRT can be traced back to more than 2000 years (See Sahota).

APRT like HPRT (Figure 5) recycles (salvages) waste from daily cell turnover (e.g. red cells at the end of their life span or white cells after dealing with invading organisms etc). Such cells do this in **a single step,** thereby avoiding the need to make our valuable ATP, which comprises 80% of our body, afresh from simple precursors, such as amino acids, by the much more energetically expensive ten step route.

APRT normally converts adenine to AMP, but when APRT is defective (broken line in Figure 5 a,b), adenine is converted by the enzyme xanthine dehydrogenase (XDH) in the liver to dihydroxyadenine (DHA) in humans. DHA is bound to the plasma *in the circulation,* but precipitates out in the kidney leading to crystals in the urine, stone formation and sometimes, severe kidney disease (see Cameron below). DHA crystals are brownish and have a characteristic circular shape as shown in Fig 6 (quite unlike most urinary crystals such as uric acid, which are needle shaped, or amorphous).

Importantly, APRT deficiency can be diagnosed from these characteristic round brown crystals in a urine deposit by anyone anywhere in the world. All that is required is a simple microscope. No expensive equipment is needed (see Fairbanks).

The clinical consequence for patients inheriting this disorder through a defective gene from both parents (see Marinaki, Sahota) is that the adenine accumulating is converted to and excreted by the kidney as the extremely insoluble DHA. This compound is even more insoluble than the poorly-soluble uric acid (solubility in water 5 milligrams per litre, compared with uric acid with a solubility itself of only 168 milligrams per litre)

Before Professor Cameron describes the clinical consequences resulting from a deficiency of APRT, it is important to look at the origin of purines such as adenine.

But where does the adenine come from?

Every day our cells turn over an amount of adenine in the form of ATP equivalent to our body weight. ATP is the power-packed molecule which all our cells need to drive cellular processes, ranging from the firing of nerve cells, to muscle contraction.

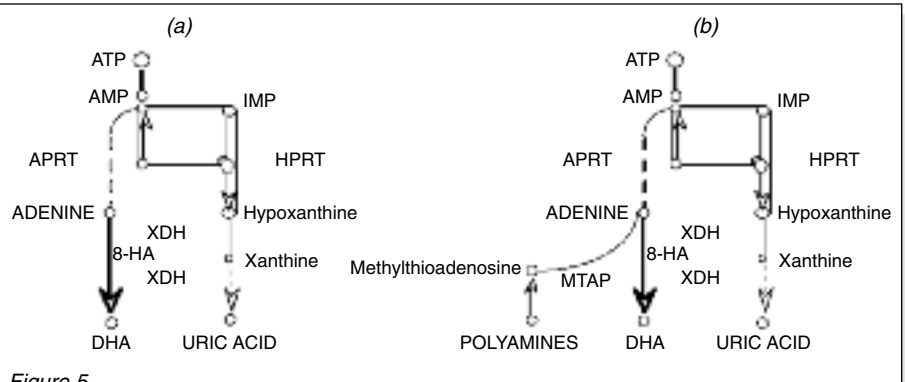


Figure 5

Until the advent of Bart, in whom we were eventually able to pinpoint the defect in APRT as the basis for the so-called 'uric acid' stones he was passing, scientists had been mystified as to why we needed APRT at all because human cells appeared to lack any route by which adenine can be made (Figure 5a).

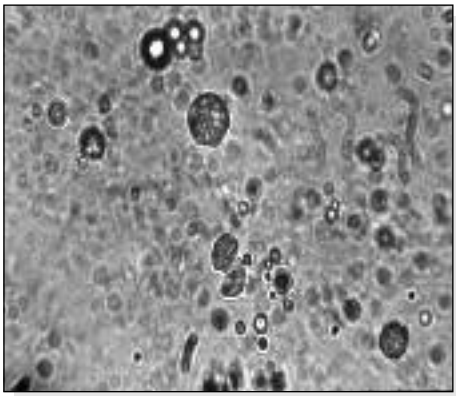
So where then did the adenine come from? (Figure 5a). A long and careful literature search revealed that the metabolism of other vital chemicals called polyamines could produce adenine as an end-product (Figure 5b). The polyamine pathway proved to be the source of the adenine, which, when APRT is defective (and thus the adenine cannot be converted to AMP) is metabolized instead by XDH in the liver, to the very insoluble DHA - the cause of the stones in Bart.

Thus, evolution had provided two alternative ways of ensuring removal of an end-product, accumulation of which might otherwise stop a clearly vital route from functioning.

Problems of laboratory diagnosis in APRT Deficiency causing DHA Stones

Dr Lynette Fairbanks

One of the first ways stone formers come to attention is through the parents, who may notice orange-brown sand on the nappies. However, it is important for parents to know that many perfectly normal healthy new-born babies excrete excess uric acid in the first few days, which may show up as orange crystals on the nappy and it is vital that the parents be advised of this (see Figure 1).



Both APRT and HPRT deficiency may show up first in this way and the important point for parents is that ***if the appearance of sand continues*** it is essential to seek expert help as soon as possible. The distinction between the three possible purine disorders causing stones or crystals can only be made by a specialist laboratory which will be able to support their diagnosis by measuring all the enzymes in red blood cells and abnormal chemicals, such as adenine and DHA in the urine, using the special chromatographic methods developed for this. The Purine Research laboratory in London is the main centre in the United Kingdom.

However, the simple and cheap test mentioned earlier, which can be made by anyone anywhere, is to examine a deposit from the patient's urine under the microscope. The presence of round brown crystals of 2,8-DHA will be an invariable finding if APRT deficiency is present (see Fig 6). These crystals are quite characteristic and very different from uric acid. However, this test will not help find carriers for the defect.

For confirmation, APRT activity is measured in disrupted red blood cells, when cells from patients of European descent in GB will have no measurable activity (Table 1), but carriers will have around 25% of the activity of healthy family members not inheriting a defective gene (see Marinarki). In contrast, most Japanese patients, carry a gene which contains a very old mutation present for more than 2000 years and

have 25% of normal activity in their disrupted red cells. Japanese patients can only be distinguished from Japanese carriers by studies using whole red blood cells, or by genetic studies, which can confirm the mutation - if it is known (see Sahota below).

It is important to know that diagnosis from red blood cells, intact or disrupted, becomes impossible to establish if a recent blood transfusion has formed an essential part of treatment, as in the 5 year old child who presented in coma in renal failure (see Simmonds below). Moreover, it may take 6 months for the transfused red cells to disappear and a diagnosis can be made. In this case fibroblast cells grown from a small skin sample will be necessary.

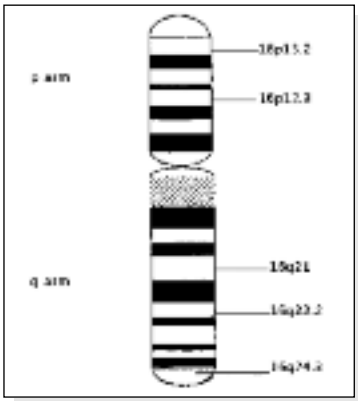
TABLE 1

	APRT activity in disrupted red cells *(nmol/h/mg haemoglobin)*		APRT activity in intact red cells *% conversion*
	Mean	Range	
Caucasian Control	24	16-32	100%
Type I deficiency			
Caucasian (GB)	0		No conversion radiolabelled adenine to AMP
Type II deficiency			
Japanese	6		No conversion radiolabelled adenine to AMP

What is the gene defect in APRT Deficiency?

Prof Amrik Sahota

The APRT gene is located near the tip of the long arm (q arm) of chromosome 16 and the gene product - the enzyme APRT - is expressed in all cells and tissues (Figure 7). Scientists use numbers such as 16.24.3 to identify the different regions of the chromosome. Dr. Fairbanks described the diagnosis of APRT deficiency by enzyme assay earlier. However, enzyme assays may not always give a complete answer. In such cases it is important to confirm the diagnosis using DNA testing. DNA analysis can identify genetic alterations (mutations), but enzyme testing is necessary to determine their biological significance. Thus, DNA testing should be regarded as a ***complement, and not a replacement,*** for enzyme testing.



APRT is a small gene, equivalent to about 3,000 beads on a string (where each bead represents one of the four DNA bases - compounds like adenine - that make up the genetic material). By comparison, the HPRT gene - which is defective in Lesch-Nyhan disease - is much bigger, equivalent to about 45,000 beads. Mutations in APRT are thus relatively easy to analyse. The standard practice is to extract DNA from a blood sample, and then to use a small portion of this DNA to make millions of copies of the *APRT* gene, using a procedure called the polymerase chain reaction (PCR) which has made it possible to carry out diagnostic testing on tiny amounts of a patient's sample.

The entire DNA sequence of the APRT gene can then be determined and compared to the normal gene to identify the mutation or mutations.

The first gene defects to be identified in APRT were in the D'hont family from Belgium. The affected child, Bart, and his asymptomatic brother Frank, each had two mutant forms (copies) of the APRT gene. One mutant copy was inherited from the mother and the other from the father. Both parents are carriers for APRT deficiency (see Marinaki), but each carries a different mutant form of the gene. DNA testing

showed that the mutant gene from the mother contains an additional base while that from the father has three bases deleted. Both changes are highly disruptive to the function of the APRT gene, which explains the lack of APRT enzyme activity in blood and other cell types from Bart and Frank. Technically, the boys are referred to as ***compound heterozygotes*** for APRT deficiency: i.e. they have two different mutant forms of the gene. As indicated earlier (see Marinaki), this type of inheritance pattern is referred to as autosomal recessive. Carrier parents do not show any symptoms of APRT deficiency, as the enzyme is sufficient to metabolise the adenine normally produced by the body.

Further enzyme studies showed that several family members spanning three generations on the mother's side had reduced APRT activity in red cell extracts (Fig 2) and were heterozygous for APRT deficiency, suggesting that the mutation must have occurred a long time ago. This mutation has been found in several other European (e.g., Austrian and German) families with APRT deficiency, confirming this is an "old" mutation. On the paternal side, only the father had reduced enzyme activity, suggesting that his mutation was, in contrast, a new one.

The D'hont family illustrates another important feature of genetic diseases in general: inheritance of a mutation does not always lead to development of disease. One boy has kidney stones, but the other is asymptomatic and completely well. These differences are unlikely to be due to diet or to factors in the environment; they likely represent the presence of genes that can modify disease expression.

Since the initial studies in the Belgian family, DNA analyses have identified many cases of APRT deficiency in Iceland, a small country. These patients have no APRT activity in their red cell extracts and contain the same mutation in both copies of the APRT gene. They are thus referred to as ***homozygous-deficient*** (as opposed to compound heterozygotes in the Belgian case) for the mutation. Genealogy studies show that all the patients are related going back five or more generations, suggesting that the mutation occurred in a common ancestor. This mutation substitutes one base for another and causes a drastic change in protein structure, completely abolishing APRT enzyme activity. The Icelandic patients all have the same mutation, but they show a wide variation in disease severity and/or age of onset, again suggesting there are other genes that contribute to the disease severity. In APRT-deficient patients of Pakistani or Middle Eastern origin, both copies of the gene contain the same mutation (homozygous deficiency). This is also likely to be due to consanguinity in these populations.

If DNA testing alone had been done in the above families, the genetic alteration would have been identified, but it would have been a difficult task to determine what this alteration did to the protein. However, enzyme testing immediately revealed that the mutation leads to loss of function of APRT, illustrating the complimentary nature of enzyme and DNA testing.

Hundreds of patients with APRT deficiency have been found in Japan, nearly 70% having considerable APRT activity in cell extracts. Thus, by enzyme assay alone such patients might be considered to be carriers for APRT deficiency, yet many have a severe form of kidney stone disease. At the DNA level it was found that this Japanese mutation decreased the affinity of the APRT enzyme for adenine. Studies in cell extracts traditionally use very large amounts of adenine as a substrate for APRT; the mutant enzyme can convert some of this adenine to the product AMP (see Fig 5). In patients, the concentration of adenine is not sufficient to react with the mutant enzyme, explaining why these patients have some activity under test tube conditions, but no activity in vivo. Thus DNA testing provided an explanation for the enzyme studies. Altogether, around 20 mutations have been described in the APRT gene.

How many individuals from a randomly selected healthy population carry a defective copy of the APRT gene? This has been estimated to be 4 to 11 per 1000, which suggests that around 1 in 33,000 to 1 in 250,000 individuals should be affected with this disorder (assuming random mating) - about 240 to 1800 people in the United Kingdom. However, this has not been found to be the case, either here, or in other countries. The explanation may be that, as described earlier, there is considerable variation in the clinical manifestation of the gene defect. This, coupled with the problems of missed diagnosis, explains why, like the elder brother Frank in the Belgian family, about 50% of APRT-deficient subjects are never recognized, many remaining trouble-free throughout life.

APRT Deficiency

Why it affects the Kidney and Urinary Tract

Prof J Stewart Cameron

Early diagnosis of APRT deficiency is important because this condition can cause serious kidney damage, including kidney failure. Although this can be avoided completely if treatment is begun early enough, if started too late then the kidneys may be damaged and no longer salvageable.

As explained above (see Simmonds), APRT deficiency causes problems because without the enzyme APRT, the body cannot get rid of the purine base *adenine*. Adenine is not itself toxic, and in particular can readily dissolve in all body fluids such as blood and urine. However under the influence of a second enzyme xanthine dehydrogenase (XDH) (Fig 5) first one, and then another -OH groups are added to the adenine molecule, leading to the formation of the very insoluble compound, 2,8-dihydroxy adenine - *or DHA* for short. The problems with DHA arise from this low solubility, so it tends to come out of solution either in tissues, or especially in the urine.

Thus blocking XDH using medicines such as allopurinol has a major role to play in the treatment of APRT deficiency.

The greater the amount of purines in the diet, the greater the amount of adenine, and thus the greater the amount of DHA produced.

Consequently, diet, and specifically a low-purine diet also has great potential to help sufferers with APRT deficiency.

Why are the kidneys affected rather than other organs? Even in complete APRT deficiency the amount of DHA is small, and it can still dissolve in body fluids such as blood, the synovial fluid in the joints and the fluid in the eye. However the body has no means of ridding itself of DHA except in through the kidneys, into the urine. This is where trouble begins: in the kidney, after being filtered, blood plasma is highly concentrated as this filtrate travels down one of the million or so tubes in each kidney, eventually to form urine. In round figures, 200 litres of fluid are filtered from the blood each day by the kidneys, but only 2 litres of urine are passed in the same 24 hours. Thus the urine is concentrated at least 100 times compared with plasma as part

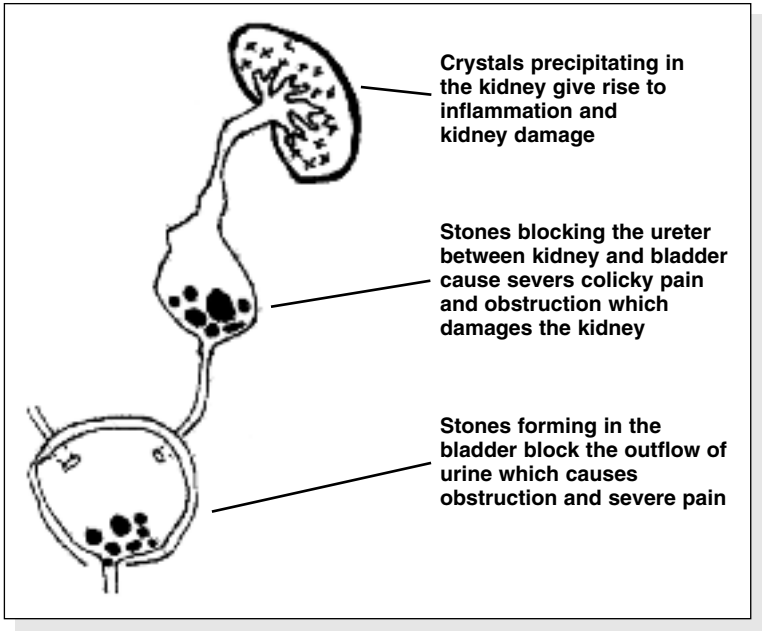
of normal functioning. In patients with APRT deficiency, this means that the concentration of DHA increases 100-fold through the kidney, and brings the concentration of DHA in the urine to levels where it will precipitate out. This is even more likely if the volume of urine passed is small because the body is short of water, especially in hot climates with a lot of water loss through sweat, or when vomiting or diarrhoea occur.

Thus the third important message is that keeping a good fluid intake helps increase urine volume, which lowers the urine concentration and helps the DHA stay in solution.

How does APRT deficiency come to attention?

Patients with APRT deficiency may vary in the way they come to attention. This is because DHA is liable to precipitate out both within the tubules of the kidney as the filtered fluid is concentrated; or after it has passed out of the kidney into the tubes from the kidney to the bladder (the ureters), or in the bladder itself.

In the kidney these events lead to either abrupt or slow kidney failure from blockage of the tubules caused by the crystals, and as well the inflammation the crystals create by irritating the kidney tissue. ***In the ureters and bladder*** **(Figure 8)** gravel and

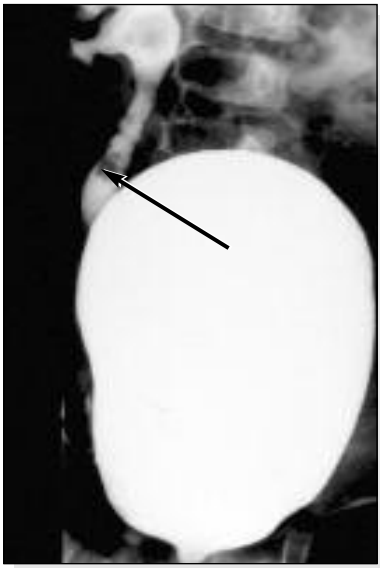


actual stones of DHA form, which can give rise to an intensely painful colic in the side which radiates downwards and inwards, or even to inability to pass urine because of obstruction in the bladder. Stones may be passed in the urine with relief of the pain or obstruction, but on occasion must be removed by intervention. These stones may be evident early in childhood, as in Bart's case; or they may not come to attention until old age. About 50% of people with APRT deficiency have no symptoms at all, like Bart's brother Frank.

Diagnosis of the kidney problems

If the sufferer has symptoms such as those just described, then it is easy to know that the kidneys are obstructed, but kidney failure from crystals in the kidney can creep up without notice. In this case, it may show up to begin with only as abnormal kidney function tests such as a raised creatinine concentration in the blood, a substance excreted by the kidney and retained in kidney failure. In addition, a *kidney ultrasound* examination may show the "bright" appearance of crystals in the kidney- although this does not tell us which sort of crystal they might be. The ultrasound tests may show also that the ureters are obstructed, or there are stones in the bladder as well, or on their own. Today X rays are used less frequently to show stones, but Figure 9 is an example of this in an infant aged only 21 months.

The stones themselves do NOT show up on the ordinary X -ray pictures, but if a radio-opaque dye is introduced into the bladder from below, as here, it shows the stones in the ureters and in the pelvis of one of the kidneys top left (the other kidney is not seen in the picture) as a gap or hole in the dye (arrow) and below this lie other stones in the ureter on its way to the bladder. These needed to be removed by surgery. The patient is now well without stones, having been on treatment including allopurinol for more than 30 years.



Unfortunately the kidney damage from crystals in the kidney is not usually reversible, although further damage can be prevented.

Figure 9
Stones of DHA in the urinary tract.

How do we treat APRT Deficiency?

Prof J Stewart Cameron

The management of APRT deficiency with kidney or stone problems follows logically from the facts reviewed earlier *(see Cameron above).*

First, a ***diet*** relatively low in purines should be taken, to minimise the amount of free adenine formed. See sheet on low purine diet on page 27.

Second, a liberal amount of ***water*** should be taken each day, and extra precautions taken in hot weather or if fluid losses occur.

However, third, the most powerful treatment of all is to use the medicine ***allopurinol.*** This inhibits the enzyme XDH and thus reduces greatly the formation of DHA. New medicines are being introduced with a similar action, such as febuxostat, which can be used if someone needing treatment is intolerant to allopurinol.

It is more difficult to know what advice to give to someone who has APRT deficiency but has had (as yet) no problems, for example other members of a family who are well but found to be affected on screening after another member has had a problem (see Fairbanks). Probably it is best to use a low purine diet and a high fluid intake alone, and reserve the use of allopurinol when (and only if) problems arise, but there may be exceptions especially if very large amounts of DHA are passed despite a low purine diet.

No treatment is necessary for someone who has only one copy of a bad APRT gene, that is, they are a carrier for APRT deficiency: they do not form stones or get kidney problems.

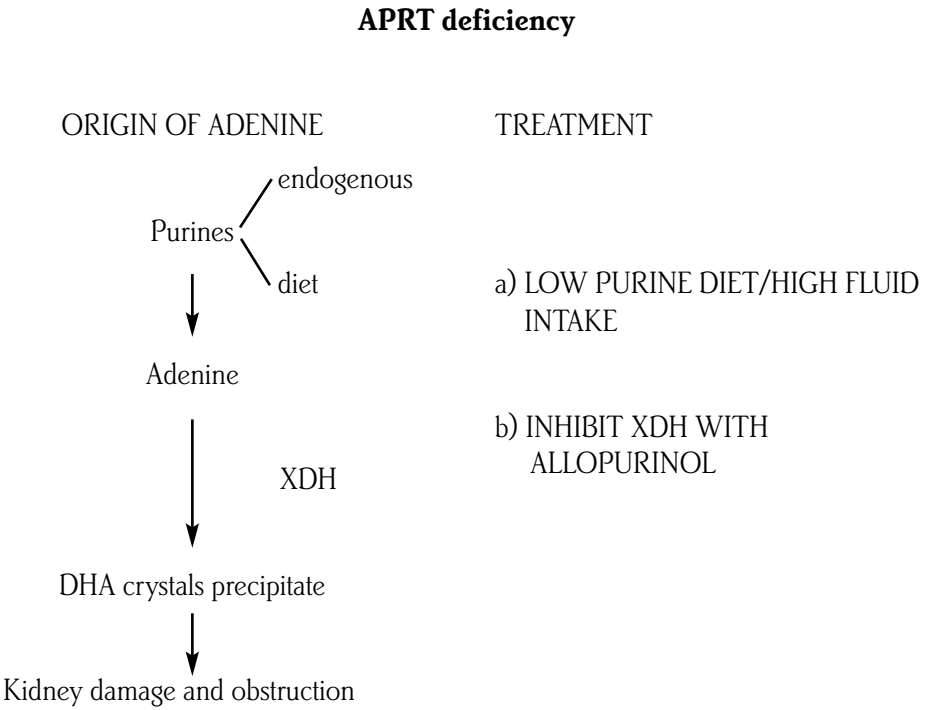
In someone with complete APRT deficiency, if stones have already formed in the urinary tract and are causing pain, infections or kidney obstruction, then they will need to be dealt with. Unfortunately we know of no way of dissolving stones of DHA, so this will mean removing them, either by a surgical operation or by disintegrating them using a machine called a lithotripter. This focuses high energy waves on the stones from outside the body. Obviously this is preferable, if it can be done, as it does not require an anaesthetic or an operation.

Fortunately, early treatment using these measures is generally completely successful

in people with complete APRT deficiency and stone problems, and relieves the affected patients of all dangers. In contrast, if the APRT deficiency is found too late when kidney failure from crystals, kidney inflammation, obstruction, or all three has already occurred, then kidney dialysis and later kidney transplantation may/will be needed, perhaps after much suffering. Several patients have even been found to have APRT deficiency only when their transplanted kidney was affected by crystals - after they had already lost their own kidney! **Such delay in diagnosis not only leads to great distress, but to huge avoidable costs to the Health Service.**

Thus the detailed preventative treatment of APRT deficient patients with kidney or stone problems follows logically (Scheme 1). First, the *diet* must be low in purines to minimise the adenine formed, Second, a liberal amount of *water* should be taken daily - much more in hot weather.

SCHEME 1



Finally *allopurinol* in a dose of 10 mg/kg per day (child) or 300 mg per day (adult) if kidney function is normal eliminates DHA from the urine. In subjects with acute or chronic kidney failure lower doses need to be used, as the drug and its active principle are eliminated through the kidneys: 5 mg/kg per day in children and 100mg/day in adults, or even on alternate days, or thrice weekly.

A high fluid intake is encouraged, and the use of allopurinol without alkali advised. For patients who have not had problems and are detected on screening, it seems best to give them only dietary advice. Fortunately early treatment is completely successful, but if found too late kidney transplant will be needed, perhaps after much suffering.

It is important to note also that if a kidney transplant is done, allopurinol needs to be given from the time of transplantation, as this may benefit the outcome in patients with APRT deficiency by preventing stones and DHA crystal damage in the graft (See Simmonds, last Chapter below).

Epilogue

Bart took his medication until the age of 16 (1989) when it was decided to stop treatment after first lowering the dose slowly. He remained stone-free until the summer of 1998 when he woke one morning with terrible abdominal pain, necessitating immediate readmission to hospital where he passed a small stone. Allopurinol was restarted immediately. Fortunately a scan showed no more stones, but Bart is back on allopurinol and has described vividly the pain of his recent stone experience as an adult.

The History of a Patient

LESSONS LEARNED?

Dr Anne Simmonds

When this "new' enzyme defect, recently identified as the cause of the stones in the little Belgian boy, was presented first at a Paediatric Nephrology meeting in Britain, a kidney specialist from the Great Ormond St Hospital for Sick Children astonished everyone by saying, "I think we may have a case like that". He was right.

Their patient was a little girl almost 5 who had been transferred from another hospital in coma in acute renal failure and had been on dialysis for 10 days. She was found to be anaemic on admission and given a blood transfusion as part of her treatment for the latter problem.

Renal ultrasound showed both kidneys were grossly enlarged (see Cameron above) and a biopsy confirmed the presence of crystals in the kidney. Many soft grey crumbly stones were removed later by surgical techniques. These stones were sent to the Purine Laboratory which confirmed that they were composed of DHA.

However, unexpectedly APRT activity in the blood was quite high - in the carrier range (see Fairbanks). Thus it was impossible to confirm that the child was APRT deficient. The reason for this finding was the normal APRT activity in the red cells of the donor blood given by transfusion. Importantly, it took six months before these donor cells disappeared completely and it was possible to demonstrate that the child was indeed completely deficient in APRT by measuring the enzyme in her blood - fibroblasts cells from the skin had had to be used to make the original diagnosis.

Thus **prior blood transfusion** is an important pitfall to be aware of when testing for possible APRT deficiency (see Fairbanks).

A family history revealed that both parents were unrelated and of Caucasian descent. The problem for this child was that mentioned by Prof Cameron (above) - DIET. This was the era of the *'flower people'* and the entire family lived on a macrobiotic vegetarian diet, rich in pulses and grains (all foods with a very high purine content (see page 27). Consequently, diet played a major role in the severity of the clinical expression of APRT deficiency in this case. From the age of two she had complained of frequent mild abdominal pains and had reportedly had a poor appetite.

Her kidney function declined and she received a kidney transplant. However she did not take her allopurinol tablets regularly, kidney function slowly declined again and she eventually progressed to needing dialysis in 2002 and received a *second* transplant in 2003.

The history of this patient is important for several reasons. It underlines:

First, the role of diet in the clinical manifestation in APRT deficient subjects.

Second, the risk of ***missed diagnosis*** if the patient has been given a blood transfusion

Third, the importance of early diagnosis of what is a potentially treatable condition when recognised early and

Fourth, compliance with diet and allopurinol treatment is equally essential. Failure to adhere to both is costly to patients and health services alike.

Finally, the value of renal ultrasonography in identifying such cases.

This case history highlights the many points that have been made by the different contributors throughout this booklet, including the fact that **all** family members must be screened for APRT activity.

The sequence of the above events confirm that, while **APRT deficiency** can be potentially fatal if unrecognized, to date **it is the *only treatable condition under the PUMPA umbrella.***

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

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

Eller P, Rosenkranz AR, Mark W, Theurl I, Laufer J, Lhotta K. Four consecutive renal transplantations in a patient with adenine phosphoribosyltransferase deficiency. Clin Nephrol. 2004;61:217-21.

Cassidy MJ, McCulloch T, Fairbanks LD, Simmonds HA. Diagnosis of adenine phosphoribosyltransferase deficiency as the underlying cause of renal failure in a renal transplant recipient. Nephrol Dial Transplant. 2004;19:736-738.

Sahota A, Tischfield J, Kamatani N, Simmonds HA. Adenine phosphoribosyltransferase deficiency: 2,8-dihydroxyadenine lithiasis. Chapter 108. In: Scriver CR, Beaudet AL, Sly WS, Valle D, eds. The Metabolic and Molecular Basis of Inherited Disease. New York: McGraw-Hill, 8th edition: 2001: pp 2571-2584.

Kamatani N, Terai C, Kim SY, Chen CL, Yamanaka H, Hakoda M, Totokawa S, Kashiwazaki S. The origin of the most common mutation of adenine phosphoribosyltransferase among Japanese goes back to a prehistoric era. Hum Genet. 1996;98:596-600.

Van Acker KJ, Simmonds HA, Potter CF, Cameron JS. Complete deficiency of adenine phosphoribosyltransferase: Report of a family. N Eng J Med 1977; 297: 127-132.

- these articles in turn contain details of a large number of other papers and chapters in books on the subject of APRT.

CONTACT ADDRESSES FOR FURTHER HELP

Information and patient support:

Mrs Joan Martin, Patient Support Group, PUMPA tel: 01293 851877

Dr Lynette Fairbanks, Dr Tony Marinaki, Purine Research Laboratory, 5th Floor Thomas Guy House, Guy's Hospital, London Bridge SE1 9RT tel: 0207 188 1276, fax: 0207 188 1280. E-mail: lynette.fairbanks@kcl.ac.uk, tony.marinaki@kcl.ac.uk

Genetic Counseling:

APRT is a treatable disorder and thus, unlike LND, APRT deficient patients do not require prenatal diagnosis (as do LND parents, where they so wish). See "Caring for Patients with LND". However, it is important (as underlined in the last chapter) for the family of all patients diagnosed as having APRT deficiency to be screened for APRT deficiency. Knowing that they are completely APRT deficient will enable APRT deficient subjects to eat an appropriate diet and avoid the progression to dialysis and transplantation/retransplantation in middle-age, reported in some families.

Also, completely deficient subjects will know that all their children will be carriers of the condition. Likewise people who are carriers will have children half of whom are like them, carriers. This information is useful also when parenthood is in prospect, as 1 in 100 or more of possible partners may also be carriers for APRT deficiency (see Sahota).

Genetic counseling is available at your nearest Regional Hospital, to which you may be referred by your GP.

For information about kidney failure

Kidney Research UK (KRUK), King's Chambers, Priestgate,
Peterborough, PE1 1FG www.nkrf.org

British Kidney Patients Association (BKPA), Bordon Hants, GU35 9JZ

Notes

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