Nephropathic Cystinosis

A guide for Parents, Patients and Healthcare Professionals

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Introduction

The information provided in this booklet is designed to help patients with cystinosis, their families, and health care providers better understand this condition and its treatment

You will be able to read, at your leisure, then write down any important questions that you may want to ask a specialist doctor or dietician.

Facts About Cystinosis

What is Cystinosis?

Cystinosis is a metabolic disease characterized by an abnormal accumulation of the amino acid cystine in various organs of the body such as the kidney, eye, muscle, pancreas, and brain. Different organs are affected at different ages.

What is Cystine?

Cystine is an amino acid. Amino acids are organic substances which when linked together form protein which is essential to life. Protein has to be metabolised or broken down in special structures within body cells called lysosomes. The different amino acids resulting from protein breakdown can again be used by the body but they must be transported out of the lysosomes.

What Causes Cystinosis?

Cystinosis occurs when its transport system fails to carry cystine thus allowing it to accumulate within the lysosomes. Accumulating cystine forms crystals which prevent the cells from working normally. The

cystine content of cystinotic cells averages 50-100 times the normal value.

How has my child got this condition?

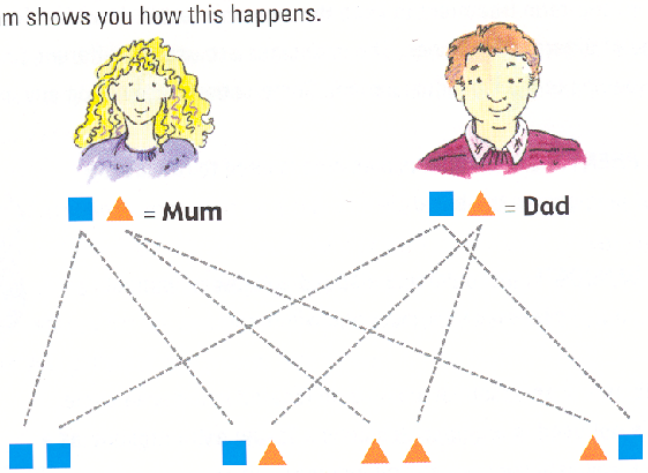
Cystinosis is a recessive genetic disorder. This means that it is not brought about by anything that may have occurred during pregnancy, neither is it an infectious or contagious disease. Genetic disorders are inherited and the pattern in which your child may have developed the condition will now be described.

If the gene is inherited from both mum and dad it is described as autosomal recessive.

Every person carries more than 30000 genes, among which there is an estimated defect in approximately seven of them. If by accident you and your partner both carry the same genetic defect (in this case for cystinosis), each time you get pregnant, there is a one in four chance that your baby will be born with cystinosis. The risk of being affected is the same for both girls and boys. The frequency of this disease is very low: 1 out of 160000 to 200000 births

How does this occur?

The diagram shows you how this happens.



In this diagram both mum and dad carry the same genetic defect (orange triangle). Each time that mum gets pregnant there is a one in four chance that the child will inherit the genetic defect from both mum and dad and will be born with cystinosis.

■ ■ = Unaffected child. Not a carrier

■ ▲ = Unaffected child. Carries the genetic fault

▲ ▲ = Child that has the condition

▲ ■ = Unaffected child. Carries the genetic fault

When a child is conceived, there is no way of predicting which sperm and which egg will unite to make the baby. At conception one egg from mum and one sperm from dad is brought together to develop the foetus. It is within the nucleus of each cell of the egg and the sperm that information recorded in the DNA is stored on strands called chromosomes. It is this information that is responsible for (predicts) the colour of the child's eyes, hair etc and will also carry the defect (any information) that relates to a genetic disease.

What are the symptoms?

There are three clinical forms of cystinosis. Infantile (or nephropathic) cystinosis; late-onset cystinosis; and benign cystinosis. The latter form does not produce kidney damage. Infantile and late-onset cystinosis differ in the age of appearance of the first symptoms and in the rapidity of the clinical course. Infantile cystinosis is usually diagnosed between 6 and 18 months of age with symptoms of excessive thirst and urination, failure to thrive, rickets, and episodes of dehydration. These findings are caused by a disorder called renal tubulopathy or Fanconi syndrome. As a consequence important nutrients and minerals are lost in the urine. Children with cystinosis also have crystals in their eyes (after one year of age) which may lead to photosensitivity. They also have an increased level of cystine in their white blood cells without adverse effect but allowing the diagnosis to be ascertained. Without specific treatment, children with cystinosis develop end-stage renal failure, i.e. lose their kidney function, usually between 6 and 12 years of age.

If cystinosis patients receive a kidney transplant and reach adulthood, their new kidney will not be affected by the disease. However, without cysteamine treatment (see section on specific treatment), they can develop complications in other organs due to the continued accumulation of cystine throughout the body. These complications can include muscle wasting, difficulty swallowing, diabetes, and hypothyroidism. Not all older patients develop these problems, however.

What is the treatment for Cystinosis ?

Periods of hospital stay are often necessary at the start of treatment, to correctly balance the different drugs. Afterwards, hospital stays are rarely necessary, surveillance is assured by out patient visits, at first every 1 or 2 months and

then 3 to 4 times a year.
Children should lead a normal life, with the drawbacks of taking medicine several times a day

Symptomatic treatment

The kidneys of children with cystinosis are not able to concentrate urine and allow important quantities of sodium, potassium, phosphorus, bicarbonate and substances like carnitine to be excreted in the urine. Treatment of symptoms compensates for these urinary losses.

Not all children are the same and may or may not present with the following symptoms. Your doctor will adapt the symptomatic treatment accordingly.

- Children need to drink large quantities of water, as up to 2 to 3 litres of water are lost in the urine every day. This explains why children feel thirsty day and night. When a child is too young to drink by themselves, water must be given every hour during the day and every 2-3 hours at night. As soon as the child reaches 8 to 10 months, they become used to drinking alone, even at night. Simply make sure that there is always a bottle of water available or at school, a flask that an adult can regularly refill. One must leave the child to drink as much as they would like.

- The loss of urinary electrolytes (sodium, potassium, bicarbonate, phosphorus) must be compensated for. Since there is a loss of salt in the urine, the food should normally be salty. It is often necessary to add a salt supplement in the form of sodium chloride. Children also lose bicarbonate and potassium in the urine, which can be compensated for by giving sodium bicarbonate and potassium bicarbonate. If the child loses little bicarbonate, but lots of sodium and potassium, a supplement in the form of sodium chloride or potassium chloride should be given. For children under the age of 4-5 years, the capsules should be opened and the contents mixed with water or another drink. Older children swallow the capsules. These supplements are divided into 3-4 daily

intakes. But the majority of children need to take at least 10-15 capsules per day, sometimes more. If the child has renal failure, urinary electrolystic loss is reduced and the supplementation doses will be adjusted by the physician accordingly.

- The child must eat correctly. Children with cystinosis often have little appetite, especially when they are young. Also some regularly vomit. Meanwhile they need to receive a sufficient caloric intake to favour growth. This explains why sometimes it is necessary, particularly before the age of 1-2 years, to give some food and medicine via a nasogastric tube or by gastrostomy. Most of the time this way of feeding is temporary.

- Indomethacin therapy (Indocid® or Endol®) is an anti-inflammatory used to treat rheumatoid arthritis and lumbago, but it can be used to reduce water and electrolyte urine loss. In children with cystinosis, indomethacin reduces the urine volume and therefore liquid consumption by about 30%, sometimes by half. In most cases this is associated with an appetite improvement, to the extent that gastric tube feeding is no longer necessary. Also, the child is woken less during the night by a need to drink or urinate. Indomethacin treatment is generally followed for several years. This drug may have some adverse effects mainly on the gastrointestinal tract.

- Rickets must be prevented or corrected. An appropriate dose of Vitamin D derivative must be given systematically. Urinary phosphorus loss entails rickets, and it may be necessary to give a phosphorus supplement.

- Carnitine is lost in the urine and blood levels are low. Carnitine allows fat to be used by the muscles to provide energy. Carnitine can be given in a liquid form once in the morning and again in the evening.

- Hormone supplementation is sometimes necessary. Sometimes the thyroid gland will not produce enough thyroid hormones. This is given as thyroxin (drops or tablets). Insulin treatment is sometimes necessary if diabetes appears. This may happen in the first months after a graft, sometimes

temporarily, when the pancreas does not produce enough insulin. These treatments have become rarely necessary in children whom are treated with cysteamine, since the treatment protects the thyroid and the pancreas. Some adolescent boys require a testosterone treatment if puberty is late. Growth hormone therapy may be indicated if growth is not sufficient despite a good hydro electrolytes balance. Therapy is composed of a growth hormone sub cutaneous injection every day (7 times a week) or 6 times a week.

Specific treatment

The aim of specific treatment for cystinosis is to reduce cystine accumulation within the cells. This goal is achieved by cysteamine treatment, which has proven effective in delaying or preventing renal failure. Cysteamine also improves growth of cystinosis children. Your doctor will be able to advise you on the procedures of obtaining this treatment.

The particularity of the drug cyteamine is to be only active a very short period of time not exceeding 5- 6 hours, explaining the need for administrating Cystagon capsules 4 times a day, that is to say every 6 hours. This treatment is also only effective if continued day after day, indefinitely in order to control the disease. It is very important to check at intervals the effectiveness of the dosage by assay of leukocyte cystine allowing to adjust the dose and to assess the compliance.

Unfortunately cysteamine may have side effects. Gastro intestinal symptoms like nausea, vomiting, abdominal pain etc. are frequent, but it seems possible to alleviate these symptoms with omeprazole (Mopral®). Breath is a problem, especially in adolescents, but it can be alleviated by different means.

Kidney transplantation has proven very helpful in patients with cystinosis, and cysteamine therapy should be maintained to try to prevent the late complications of the disease

For both young children with cystinosis and older patients with a kidney transplant, cysteamine eyedrops may be available to remove the corneal cystine crystals. Cysteamine eyedrops should be applied regularly, day after day, indefinitely to reverse corneal crystal accumulation (any eye damage) and prevent future problems. Cysteamine eyedrops have not yet obtained a market authorisation. Your doctor will be able to advise you on the administration and on how to obtain this product

Treatment compliance

It is difficult for children with cystinosis, as they are obliged to take a lot of medication, of which cysteamine must be taken every 6 hours. But we know that with correct treatment, the child will be well and renal failure will be delayed. While insufficient treatment means that there will be complications during childhood or adulthood. As well as this, if the child has a renal transplant, anti-rejection treatment must be taken, and the cysteamine must be continued to protect other organs.

The child or adolescent is sometimes tempted not to take the cysteamine.

The expression “good compliance” describes the fact that the medical prescription is respected, whether it be a medical treatment, taken in correct doses and regularly, or other prescriptions such as a diet, or respecting an appointment with the doctor. “Poor compliance” to the contrary describes medical prescriptions that are not respected and medical treatment that is not taken regularly.

Children with cystinosis may have periods of poor compliance, as with all chronic illnesses. This is exceptional in small children, who amazingly easily accept all the drugs. Compliance difficulties are more frequent during adolescence.

How are compliance problems prevented, and how to re-establish a normal regime after a period when the drugs have not been taken regularly?

- The information given to parents when the child is still small is essential: information on the disease and its consequences, the role of each drug, the complications when the drug is not taken. It is the responsibility of the parents to make sure that the child takes all the drugs. A lot of courage, availability and will power are needed. To take the drugs, the young child needs to sense the parent's authority. It must be tempting for parents to lighten up sometimes, but this should not be done.

- As much information as possible should be provided, especially since there has been so much progress over the last years in cystinosis and there will be more. It is known that correct treatment delays the consequences of the disease. Complications observed 20 years ago (thyroid gland, pancreas, liver deterioration) are no longer seen thanks to cysteamine treatment. It is also thought that the later muscular and neurological complications may be delayed by treatment.

- It still remains necessary to help the parents and child by means that may seem secondary, but they are vital. It is not so easy to swallow in the morning, at lunch and in the evening a dozen different drugs. The following may help good compliance:
  - The use of weekly pillboxes, prepared on Sunday.
  - A pillbox with alarm.
  - Products that correct or help the breath and body odour.

Particular problems during adolescence

- At adolescence, the parents and paediatric team must progressively release their protection, and help the child to take on their own responsibly. The following principles are useful :
  a. The adolescent should be considered as an active partner: with the right to discuss, negotiate, argument, and also error.
  b. Information should be given on the disease, the role of different drugs, the expected results, and possible side effects.
  c. Do not use threats or induce fear, which increase anxiety.
  d. Doubts on treatment compliance are raised by the systematic monitoring of the leucocyte cystine. But it is important to use these data after speaking carefully to the adolescent.
  e. Do not blame an adolescent who is not compliant, but instead listen: an adolescent not taking the treatment is an adolescent who needs to be helped in every possible way.

- Despite all the willingness of parents, doctors and the healthcare team, real difficulties still appear: it is as though the adolescent, well informed, doesn't have the courage to look after themselves. Periods of complete opposition to the parents or doctors begin and communication becomes difficult. Everyone feels guilty, overtaken by the event. These compliance problems are never just a simple lack of education on the disease or treatment but can be the expression of adolescence in which rebellious periods are expressed by poor treatment compliance. Other adolescents without cystinosis find other ways of expressing themselves that are sometimes just as dangerous.

  These difficult periods come about in a climate of deep insecurity mixed with anguish, feelings of injustice, revolt, denial, guilt, isolation, concern related to the corporal image or sexuality, depression. Help

from a psychologist or psychiatrist is necessary to decode the real meaning of poor compliance and help the child and family to get through the situation. These problems are never the child's or parent's "fault" and it is important that they should not feel guilty. These situations are never desperate, if the child and family accept to be helped.

In practice, the child, parents, family, school entourage, and medical team all move ahead together. Everyone cooperates with each other. Of course there are ups and downs but most of the time the child becomes, like any other, and despite the illness, a young man or young lady looking to the future, that is to say an adult that manages their life.

Is Prenatal Detection Available?

Each time that a man and woman both carrying the genetic defect decide to have a child, there is a one in four chance that the child will inherit the genetic defect and be born with cystinosis (see section on "how has my child got this condition").
Prenatal diagnosis is available for families known to be at risk for having a child with cystinosis. Chorionic villus sampling is performed at 8-9 weeks of gestation; amniocentesis can be performed at 14-16 weeks of gestation. It is important to carefully discuss this subject with a specialist doctor who will be able to advise you according to your situation.

What are possible future developments?

Much remains to be learned about cystinosis. Investigators have identified the (abnormal) gene and the mutations which cause this

condition and have created a mouse model of the disease. Other investigators are trying to understand the mechanisms of cell dysfunction and to determine the best therapies for each complication. Some questions which remain include:

- Will children with cysteamine from infancy be spared all of the later complications of cystinosis?
- Will they avoid the need for kidney transplantation entirely?
- To what extent will cysteamine benefit patients who begin therapy after receiving a kidney transplant?

Glossary of terms

Amniocentesis:	withdrawal of a sample of amniotic fluid (the fluid surrounding the fetus in the uterus). This fluid contains cells from the fetus which can be examined for abnormalities
Chorionic Villus Sampling:	a technique in which a sample of chorionic villus (the outer membrane surrounding a fetus) can be obtained between the 8th and 12th weeks of pregnancy. The cells from this sample can be examined for abnormalities.
L-Carnitine:	L-Carnitine is used by the body to transport long chain fatty acids to the mitochondria in cells, where it is burned for energy. Since this fat burning is such a major source of muscular energy, deficiencies in carnitine are manifested as low energy levels and muscular weakness.
Electrolyte:	a substance that produces ions (atom or group of atoms which can conduct electricity) eg sodium, potassium, chloride, bicarbonate.
Enzyme:	a protein which activates a chemical process without being changed by that process. Enzymes are relatively specific therefore there are large numbers of these involved in many different reactions within the body.
Gastrostomy Tube:	a flexible tube placed during a surgical operation directly through the skin of the abdomen into the stomach. It can remain in place for a long period of time and can be used for the administration of fluids, medication and feeds.
Hormone:	a substance produced in one part of the body which passes into the bloodstream and is carried to other parts of the body where it acts to change their structure or function.
Lysosome:	a particle in the cytoplasm (jelly-like substance) within cells which is bounded by a single membrane. It contains enzymes which are responsible for breaking down substances in the cell.
Phosphate (Phosphorus):	a non-metallic element which is a major constituent of the tissues of humans particularly bones.
Rickets:	a disease in which bones do not harden due to a deficiency of vitamin D. Because they are soft they bend and this can be seen especially in the long bones or the front of the ribcage.
Transplantation:	the implanting of an organ from one body to another.

Useful addresses

Cystinosis foundation

USA
604 Vernon Street
Oakland, CA 94610
www.cystinosisfoundation.org
The Cystinosis Foundation is an all volunteer, non-profit organisation dedicated to providing services for those suffering from cystinosis.

Australia
http://australia.cystinosis.com/contacts.htm

Germany
http://www.cystinose-selbsthilfe.de/

Mexico
http://www.cystinosisfoundationmexico.cjb.net/
Mar de China 44 #1 Altos. Col. Popotla
México, D.F., C.P. 11400, Tel: (01 55) 53 41 96 64

Netherlands
http://stofwisselingsziekten.nl/cystinose/
cystinose@wanadoo.nl

UK
Charity No.1074885.
Founder: Jonathan Terry
jonathan@cystinosis.org.uk
www.cystinosis.org.uk

Orphan Europe

60, avenue du Général de Gaulle

92046 Paris La Défense – France

www.orphan-europe.com

If you have any queries regarding your treatment or any other aspect of cystinosis please contact your doctor.

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