

Classical Homocystinuria

A guide for **parents, patients** and **families**



www.e-hod.org

Introduction

You or your child have/has been given the diagnosis **homocystinuria**, (also called 'classical homocystinuria').

Initially any information regarding conditions like homocystinuria is hard to understand, especially at a time when you are naturally very worried and suddenly provided with lots of medical information.

By describing this condition in a booklet format, you will be able to read it at your leisure, and then write down any important questions that you may want to ask your **specialist doctor, nurse, or dietician.**

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How the body deals with protein ?

Foods containing **protein** are **eggs, milk, fish, meat, cheese, bread** etc. During digestion, protein is broken down into smaller molecules or “**building blocks**” to be transported in the blood and used for growth and tissue repair.

What started as a steak or a glass of milk will have now been broken down into 20 individual “building blocks” known as **amino acids**. These amino acids travel in the blood stream and are supplied to the cells where they are needed. One of these amino acids is called **methionine**.

If there is more methionine than the body needs, the extra methionine is broken down. **Homocysteine** is formed during the break-down of methionine.

Figure 1: Ingested food is broken down into its various components

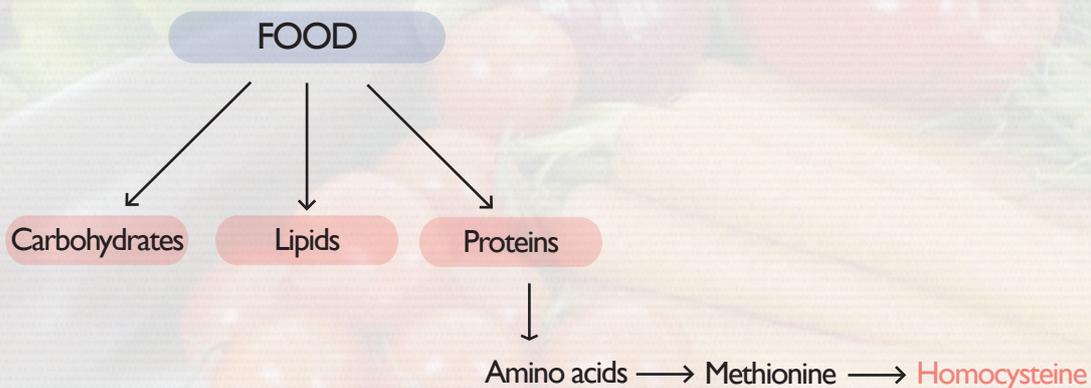


Figure 1

Methionine and homocysteine break-down

The break-down of methionine is complicated. **Homocysteine** is formed during the break-down of **methionine**; it is then either broken down further into a harmless substance called **cystathionine** or it is recycled back to **methionine**. **Enzymes** are the things that make chemical reactions happen in the body. The conversion of **homocysteine** to **cystathionine** requires an enzyme called **cystathionine beta synthase (CBS)**. To work efficiently, this enzyme requires **vitamin B6 (pyridoxine)**. If the CBS enzyme is not working efficiently, there will be a **build-up of homocysteine** (and also methionine) in the body. It is this **accumulation of homocysteine** that causes health problems and leads to the disease called **homocystinuria**.

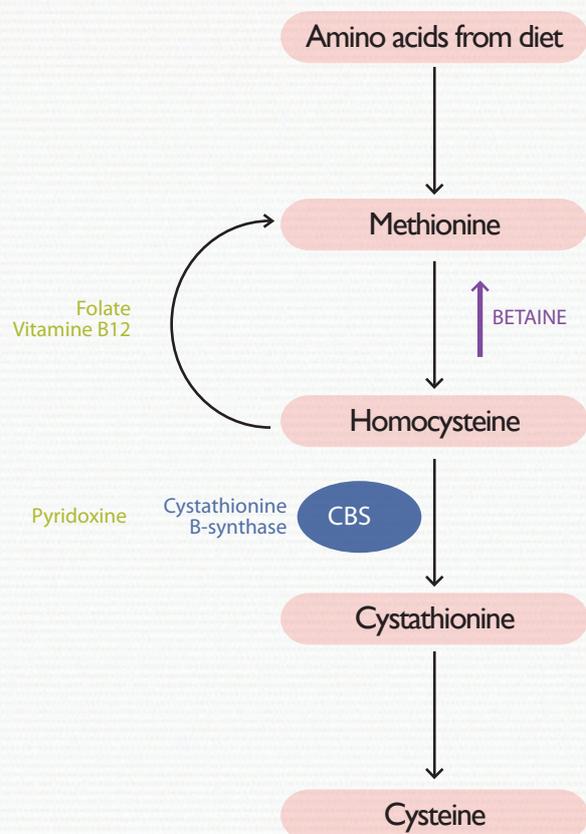


Figure II : methionine metabolism

Homocystinuria

“**Homocystinuria**” means the presence of **Homocysteine** in the **urine**, which occurs when **blood homocysteine levels are high**. There are several different types of homocystinuria caused by different faults in methionine metabolism. Classical Homocystinuria refers to the type in which **CBS (Cystathionine B-Synthase) is not working** (see figure 2).

What are the symptoms ?

Symptoms vary from person to person and may occur at different ages. Babies born with homocystinuria will generally appear **normal at birth**. In several countries, homocystinuria may be detected on the newborn blood screening program.

Homocystinuria causes a wide range of symptoms, which can start to develop progressively from a few months of age. The most common symptoms mainly affect four systems of the body: The **eye**, the **brain**, the **bones** and the **vascular** (blood-vessel) **system**. The most common eye symptoms include severe **short sightedness** (myopia), **dislocation of the lens** (ectopia lentis) and **glaucoma**. Eye symptoms are often the earliest signs of the condition and may bring the underlying diagnosis to light. Homocystinuria may also cause **developmental delay** and **learning difficulties** and in untreated older patients **psychiatric problems** have been reported. Very high homocysteine levels increases the blood's tendency to clot and therefore even young people with homocystinuria may develop athero or venous thrombosis which may present as strokes, heart attacks and vein thrombosis. There are also some **skeletal effects** seen ; such as it has been noticed that untreated patients are often taller than average and have long arms and legs. Early **osteoporosis** may also be seen in affected men and women.

It is important to note that early treatment can prevent many of these symptoms from occurring or prevent worsening of symptoms that may be present at the time of diagnosis.

The above list is by no means exhaustive. Patients with homocystinuria may develop a wide range of symptoms and not all patients develop the same symptoms.

Treatment

Aims of treatment

The **age** of initial diagnosis of homocystinuria and the **severity** of the condition will determine the different treatment aims.

In newborn babies diagnosed with homocystinuria, the aim is to **prevent the development of symptoms** and to **ensure the development of normal growth and intelligence**.

When the diagnosis is made later in life when some symptoms have already developed, the aim is to prevent further complications such as thromboembolic events (like strokes or heart attacks) and to prevent worsening of symptoms which are already present.

In order to achieve these clinical aims, **all treatment options are targeted to reduce homocysteine levels in the blood**.

The type of treatment for homocystinuria largely depends on whether the affected individual's homocysteine levels respond to pyridoxine (vitamin B6) treatment and homocystinuria is often categorized into 2 types:

1. *Pyridoxine responsive homocystinuria*
2. *Pyridoxine non-responsive homocystinuria*.

Upon diagnosis, all new patients with homocystinuria are given a trial of pyridoxine treatment to establish whether they are responsive or not before starting any dietary treatments.

1. Pyridoxine responsive homocystinuria

For individuals that have been found to be pyridoxine responsive (i.e. their homocysteine values drop dramatically with pyridoxine treatment), high doses of pyridoxine (vitamin B6) will be the mainstay of treatment. Side effects are rare; however, you should consult your doctor if you are worried.

2. Pyridoxine non-responsive homocystinuria

For patients who do not lower their homocysteine levels when treated with just pyridoxine, additional treatment options will be needed. An individually tailored treatment plan will be initiated and controlled by an experienced physician in order to achieve the best possible result for each patient.

A patient may therefore receive some or all of the treatments listed below.

A) Methionine restricted diet: A methionine restricted diet to reduce the high homocysteine levels is often used for the treatment of pyridoxine non-responsive homocystinuria. This particular diet will be prescribed by a doctor in conjunction with a dietician and will be monitored regularly and modified according to blood levels of homocysteine and methionine. There are 3 components to the diet:

- i) Avoidance of high protein foods such as meat eggs etc but as methionine is an essential amino acid small measured amounts of naturally occurring protein will be necessary for normal growth and development. The amount of protein needed is tailored to each patient.
- ii) Methionine-free protein substitute drink - A specially formulated drink is made with all other amino acids except for the one that increases homocysteine - methionine. As the small amount of natural protein allowed in the diet is not sufficient to meet our daily requirements of protein, this special drink (synthetic protein) is a very important part of the diet as it provides all the other amino acids required by your body in proteins without the 'harmful' one. Cysteine supplements may also be needed as this amino acid is often low in people with homocystinuria.
- iii) Low protein and protein-free foods including fruits, vegetables and commercially available low protein products e.g. low protein flour/ bread/ pasta/milk etc. These so called 'free foods' can be consumed without restriction.

B) Vitamin supplementation with pyridoxine, folic acid and vitamin B12: The aim of supplementing these vitamins or cofactors (pyridoxine, folic acid and vitamin B12) is to optimise the enzyme activities of methionine metabolism, as the enzymes involved require these vitamins to work efficiently. (See figure 2). These supplements are usually given orally although B12 injections may be needed intermittently.

C) Betaine is a naturally occurring food substance that activates a different enzymatic pathway, (sometimes called a recycling pathway) and reduces homocysteine levels by re-converting it back to methionine.

It is very important that you take all your medication as prescribed by your doctor.

Why do I or does my child have this condition ?

Classical homocystinuria is a **genetic condition**. This means that it is transmitted through the genes and not brought about by anything that may have occurred during pregnancy. Genetic disorders are **inherited** and there are different inheritance patterns. The pattern of inheritance for homocystinuria is called **autosomal recessive** which means that a **gene defect is inherited from each parent**. In other words, **both parents are carriers for homocystinuria**.

People who carry one normal CBS gene and one mutated CBS gene (homocystinuria) are called **“carriers”**. Carriers are well and normally do not have any symptoms of the condition. When both parents are carriers, they have a 1 in 4 (25%) chance in each pregnancy that the child born will have homocystinuria. There is also a 1 in 2 (50%) chance that the baby is a carrier, like the parents, and a 1 in 4 (25%) chance for the baby to have inherited two normal genes.

The diagram shows how this happens :

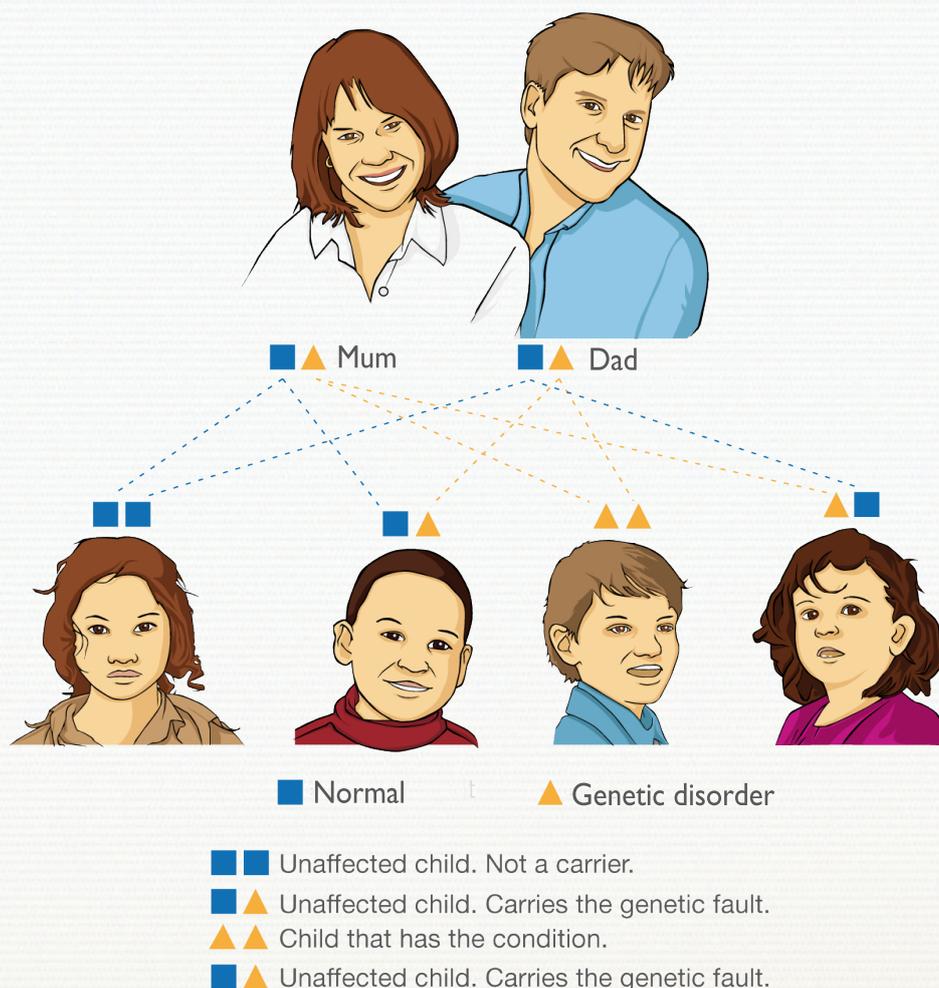


Figure III

What does the future hold for my child ?

As previously described, the way homocystinuria presents is very variable. It is however a **lifelong condition** that requires **lifelong treatment, monitoring** and **specialist clinic visits**.

For newborns diagnosed and treated from soon after birth, the long term outcome is excellent with minimal complications expected if the child has optimal metabolic control. **Consistent good metabolic control in adolescence and adulthood** ensures the best chance of a normal healthy life.

In some people, the condition is not diagnosed until later in childhood or in early adulthood so there may already be problems established such as **learning difficulties** and **eye problems**. **Treatment** to control homocysteine levels however is just as important in these individuals, to prevent worsening of any symptoms already present and to prevent them from getting other complications such as stroke.

There are now many adults, who were diagnosed with homocystinuria as newborns over 30 years ago, living normal lives, establishing their own families, participating in third level education and working in all sorts of occupations.

Your doctor may be able to put you in touch with other affected families if you so wish.

Pregnancy

Where possible all pregnancies should be planned and care provided pre-conceptually with your specialist consultant.

During your pregnancy, care will be shared between your **specialist consultant** and your local **obstetric team**. This ensures that throughout pregnancy both mother and baby are provided with the maximum support available. It is likely that you will be monitored more closely and some of the treatment, maybe the diet or medication, will be changed.

Poor metabolic control during pregnancy **increases** the risk of **complications**, in particular of miscarriage and thrombosis, therefore control of homocysteine levels is particularly important, and **blood thinning agents** may be prescribed (in conjunction with a haematologist) in order to reduce the risk of thrombosis during the pregnancy and up to 10 weeks afterwards.

However by adhering to the treatments prescribed, potential complications can usually be prevented and a good outcome for both mother and baby can be expected and many successful pregnancies and births have been reported.

Women on birth control pills should seek advice from their physician if they are diagnosed with homocystinuria, as the increased risk of thrombosis due to the disease may be enhanced by taking contraceptives.

Long term outcome of treated patients with homocystinuria

Patients who were **diagnosed** by **newborn screening** or very **early in childhood** and who received early **treatment** and good biochemical control have been shown to live and enjoy a **normal life**.

For those who **already showed symptoms** at the time of **diagnosis**, **treatment** with good biochemical control has been shown to **stop further escalations of the symptoms** and **improve the quality of life**.

Should you require extra assistance with complying with your treatment, you should seek help from your doctor.

Travelling

Travelling should provide no barriers to the person with homocystinuria but it is wise to take **sensible precautions** if planning an extended trip or if going abroad.

It is sensible to check that your **destination has suitable medical facilities** should you become ill whilst away.

It is absolutely necessary to continue with your **diet** and **medication** whilst away and to ensure that you have **adequate supplies** to last you for your trip.

Should a long haul flight be planned please discuss with your physician as extra precautions may be required to **prevent thrombosis** - such as ensuring you take plenty of fluids during the trip, using flight stockings (available from pharmacies), staying mobile and avoiding any sedating agents (such as sleeping tablets or alcohol).

You should carry some information regarding the nature of your illness as homocystinuria is a **rare condition** and many doctors will not have encountered it before. This can be provided by your clinical team. For longer periods abroad, your medical team may be able to suggest a local doctor that could supervise your care.

Glossary

Amino acids : the building blocks of proteins

Newborn screen : a blood test done on babies in the first few days of life looking for various genetic/metabolic disorders. Some countries include pyridoxine non-responsive homocystinuria in this screen.

Enzyme : a protein in the body that makes the chemical reactions proceed more quickly

Co-factor : a naturally occurring compound (a vitamin) that is needed by an enzyme to work properly

Orally : by mouth

Paediatrician : a doctor who trains specifically in the care of children

Methionine : an amino acid that is converted in the body to homocysteine

Homocysteine : the amino acid that is elevated in homocystinuria

Cystathionine beta synthase (CBS) : the enzyme that is deficient in homocystinuria

'Good metabolic control' : where homocysteine levels are maintained within the desired range so as to minimise complications



For more information and contacts of patient organisations :

www.e-hod.org

www.climb.org.uk

www.rarediseases.org

If you have any queries regarding your treatment, or any other aspect of homocystinuria, please contact your **consultant, clinical nurse specialist, dietitian, or doctor.**

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For more information : <http://ec.europa.eu/eahc/news/news211.html>

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