EHOD
European Network and Registry for Homocystinurias and Methylation Defects

Remethylation disorders

Cobalamin defects and severe MTHFR deficiency

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

Contents

Introduction

You or your child have/has been given the diagnosis of a **disorder of remethylation**. Several disorders belong to this group and their names are listed here:

Cobalamin C (cblC) defect
Cobalamin D (cblD) defect
Cobalamin E (cblE) defect
Cobalamin F (cblF) defect
Cobalamin G (cblG) defect
Cobalamin J (cblJ) defect
Severe 5,10-metheylentetrahydrofolate reductase (MTHFR) deficiency

The defects underlying remethylation disorders are located in the **metabolism of two vitamins** which are essential to the body. **Cobalamin** is another name for **vitamin B12** and **MTHFR** is an important player in **folate metabolism**.

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

By describing these conditions in 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.

Metabolic function

To be a fit healthy individual, we have to feed our body regularly to provide **energy and repair tissues.**

The foods that we eat are broken down into small packages and either used for growth and repair, stored to be available for periods of starvation, or disposed of as waste. Although this explanation describes the basic process, it is of course much more complex.

How the body deals with the 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**.

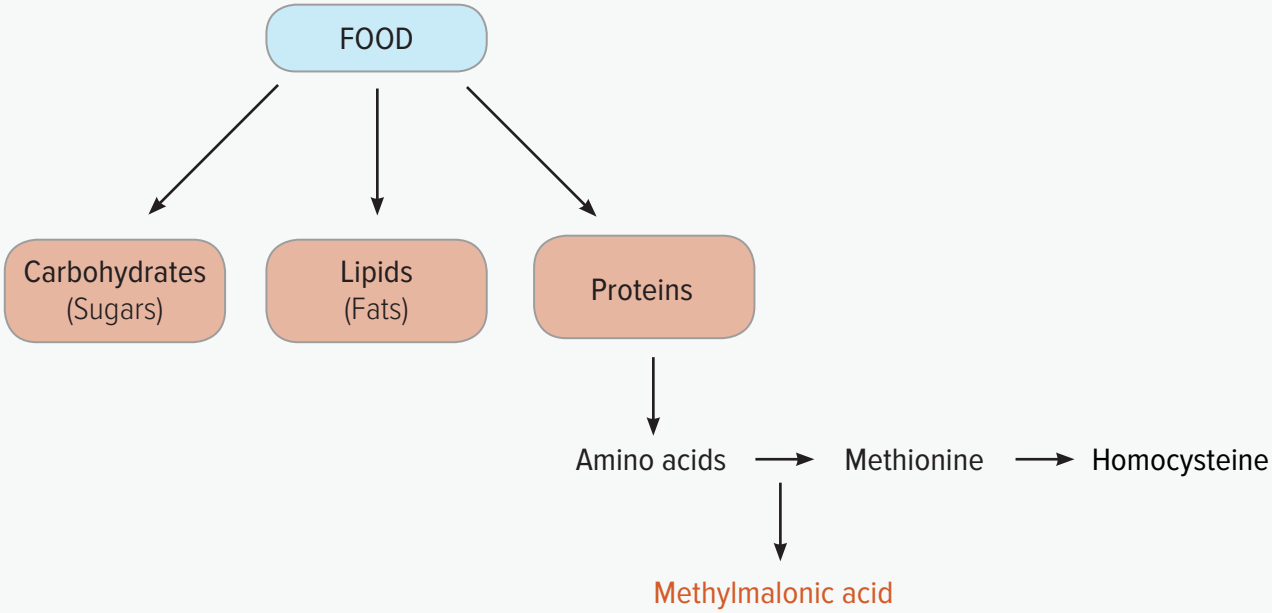
What started as a steak or a glass of milk will have now been broken down into 20 individual **"building blocks"** known as **amino acids**. These amino acids travel in the blood stream and are supplied to the cells where they are needed. One of these amino acids is called **methionine**.

Most amino acids can be made by the body itself however some are not made by the body and therefore are essential in the diet. Methionine is one of the **"essential amino acids"**.

When food is eaten and the proteins are broken down into its amino acids, methionine becomes metabolically available. In this so called "methionine metabolism" homocysteine is formed.

Additionally, a substance called **methylmalonic acid** ("MMA") is derived from methionine and other essential amino acids such as isoleucine, valine and threonine.

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

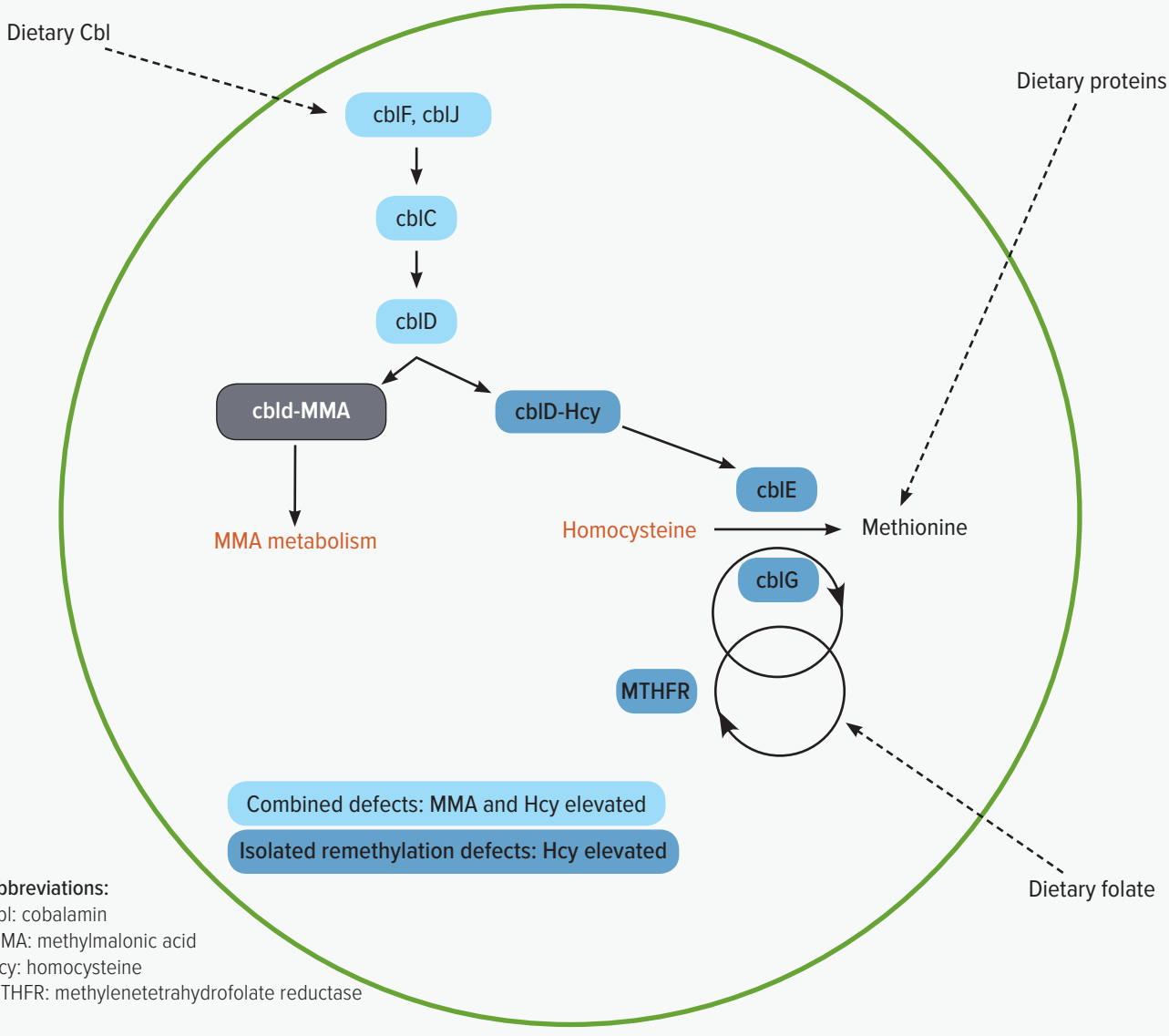


Methylation pathways of methionine, homocysteine and methylmalonic acid

The metabolism of methionine is complex, dependent on many steps and it produces different intermediary products, one of which is homocysteine. Homocysteine is then either broken down into a harmless substance called cystathionine or is recycled back to methionine. There are different enzymes required for the process to work. Some enzymes require a vitamin (or "cofactor").

The metabolism of the other important intermediary product, MMA, is located in the mitochondria, the cell's power plants.

Figure 2: Defects in cellular cobalamin and folate metabolism, causing remethylation disorders



Abbreviations:
Cbl: cobalamin
MMA: methylmalonic acid
Hcy: homocysteine
MTHFR: methylenetetrahydrofolate reductase

Remethylation disorders

Remethylation disorders share the problem that homocysteine cannot properly be recycled to methionine. Because of this, **homocysteine remains high and methionine is low** in blood.

The main problem shared by all remethylation disorders is that the loop of methionine from food becoming homocysteine and then becoming methionine again is interrupted. This so-called homocysteine-methionine pathway produces important substances (methyl-groups) which are needed in many other metabolic pathways of the body. If the homocysteine-methionine pathway is interrupted these methyl groups cannot sufficiently be provided. Consecutively, other important functions of the body are disturbed. Additionally, high homocysteine itself may cause health problems.

Some of the remethylation disorders result in an additional problem: they impair the disposal of **methylmalonic acid (MMA)** from body cells. In these diseases MMA is also high in blood and urine and can cause additional health problems.

The cblC defect, the cblF and the cblJ defect affect both the homocysteine–methionine and the MMA pathway. Individuals affected by the cblD defect can either have such a combined defect or isolated problems of the homocysteine-methionine or the MMA pathway. Which variant the disease presents with depends on the location of mutations on the gene responsible for the cblD defect.

Severe MTHFR deficiency as well as the cblE and cblG defects perturb the homocysteine–methionine pathway only; thus MMA is normal in affected individuals.

What are the symptoms?

Symptoms vary from person to person and may occur at different ages, even in adolescence or adulthood. Babies born with a remethylation defect mostly will appear normal at birth but some children may have health problems very early in life.

Remethylation defects cause a **wide range of symptoms**, which can start to develop progressively from a few days of age.

The most common symptoms mainly affect four systems of the body: **the eye, the brain, the vascular (blood-vessel) system and the kidneys.** The most common eye symptoms are retinal and optic nerve changes which might result in impairment or even loss of vision. Developmental delay, learning difficulties, behavioural problems and, in untreated older patients, psychiatric problems and dysfunction of the peripheral nerves (neuropathy) have often been reported. Brain imaging may show changes of the white matter and / or the brain may be smaller than usual. Very high homocysteine levels increase the blood's tendency to clot. Therefore affected individuals may develop venous thrombosis or pulmonary arterial hypertension. Acute kidney problems or chronic renal failure occur mostly in untreated patients and may be the first sign of the disease.

Macrocytic anaemia which means a low number of enlarged red blood cells is often seen in untreated patients. An exception is severe MTHFR deficiency, in which macrocytic anaemia occurs very rarely.

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

Most of our knowledge about the response of remethylation disorders to treatment is derived from experience with the **cblC defect**, the most frequent of the remethylation disorders. It is important to note that **early treatment can prevent many of the symptoms** listed above from occurring or prevent worsening of symptoms that may be present at the time of diagnosis. However in the cblC defect affections of the brain, cognitive impairment and eye disease do not respond as well to treatment as other symptoms and may even be progressive. In severe MTHFR deficiency the brain seems to respond better to early treatment than in the cblC defect.

Treatment

Aims of treatment

The age of initial diagnosis of remethylation disorders and the severity of the condition will determine the different treatment aims.

- In newborn babies diagnosed with a remethylation defect the aim is to prevent the development of symptoms.
- When the diagnosis is made later in life when some symptoms have already developed, the aim is to prevent further complications and worsening of symptoms which are already present.

In order to achieve these clinical aims, all treatment options are targeted to reduce homocysteine, and normalise methionine and eventually MMA levels.

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

A) Injections of hydroxocobalamin. In the remethylation disorders based on dysfunctions of the cobalamin pathway, high doses of hydroxocobalamin are injected, mostly intramuscular. Unfortunately the orally available forms of cobalamin are not effective in these disorders but may be sufficient in severe MTHFR deficiency.

B) Betaine is a naturally occurring food substance that activates a different enzymatic pathway, and reduces homocysteine levels by re-converting it back to methionine. Betaine is used in all remethylation disorders.

C) Folic or folinic acid are used as adjunctive therapy to restore cellular and cerebral folate deficiency in severe MTHFR deficiency. In all other remethylation disorders, the aim of supplementing folic acid is to optimise the enzyme activities of methionine metabolism, as the enzymes involved require this vitamin to work efficiently. (See the methionine metabolism figure on page 5 to see where they work).

D) Carnitine may be given to avoid carnitine deficiency in disorders with elevated MMA

It is very important that you take all your medication as prescribed by your doctor. Should you require extra assistance with complying with your treatment, you should seek help from your doctor.

Drugs to be avoided

In all individuals affected by a remethylation disorder use of nitrous oxide (N2O) in anaesthetic procedures is to be avoided for its inhibition of enzymes involved in remethylation.

Why do I or why does my child have this condition?

Remethylation disorders are genetic conditions. 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 remethylation disorders is called **autosomal recessive** which means that a gene defect is inherited from each parent. In other words, both parents are carriers for the remethylation disorder.

People who carry one normal gene and one mutated or "disease-causing" gene 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 the disease. 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.

How does this occur?

The diagram shows you how this happens (Figure 4).

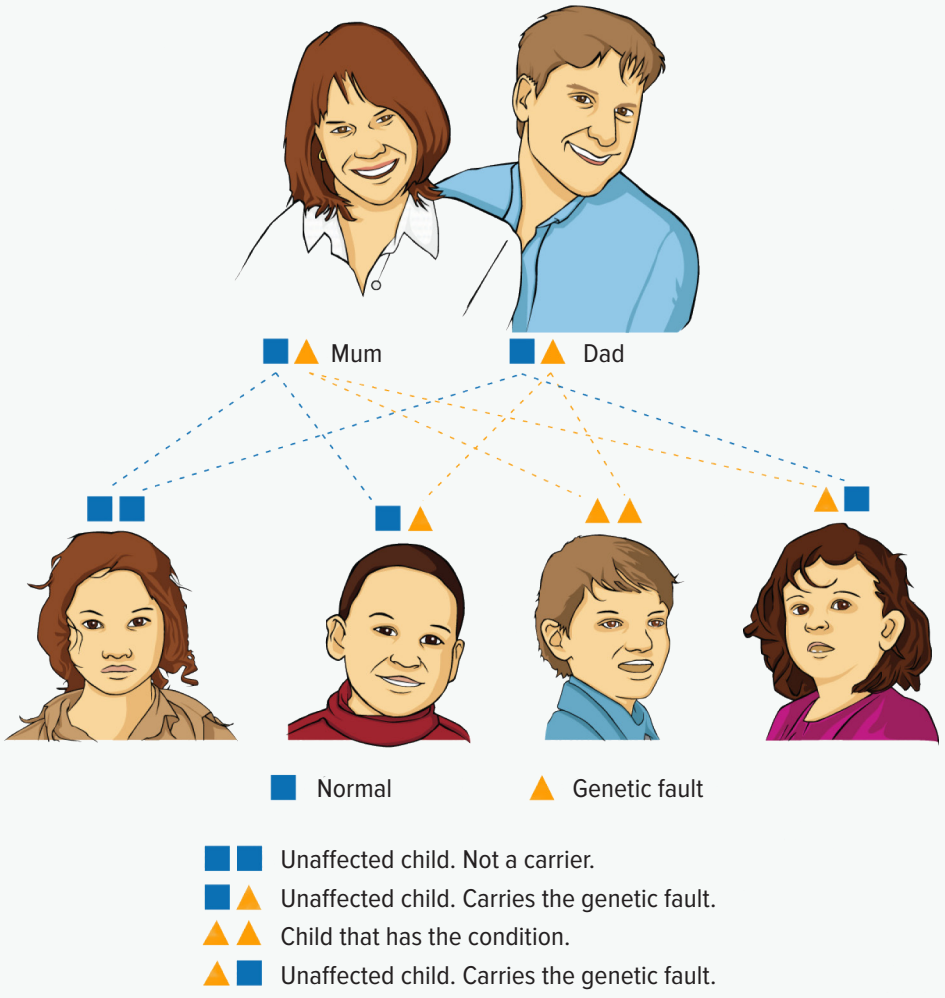


Figure 4. Mode of inheritence of inherited methylation disorders

At conception it cannot be predicted which egg and sperm will join to form the baby. Each egg and sperm carries half of all of the baby's genes i.e. each egg will carry one copy of a gene and each sperm similarly will carry one copy of a gene. It is random whether the copy of a gene will be the copy with the defect or the normal copy. When both the egg and the sperm have defective copies then the baby will be affected by the disease.

What does the future hold for my child?

As previously described, the way remethylation disorders present 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 generally better. Consistently good metabolic control ensures the best chance to avoid complications. However in severe forms of the disorders even with good metabolic control the disease may not improve or even progress.

In some people, the condition is not diagnosed until later in childhood or in early adulthood so there may already be problems established. Treatment however is just as important in these individuals, to prevent worsening of any symptoms already present, to prevent them from getting other complications and improve the quality of life.

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

Pregnancy

It is advised that all females affected by remethylation disorders involved in sexual relationships be adequately protected with suitable contraception. Where possible all pregnancies should be planned and care provided pre-conceptually with your Specialist Consultant.

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

Travel

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 locally should you become ill whilst away.

It is absolutely necessary to continue with your 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 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 remethylation disorders are rare conditions 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

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

Intramuscular: into the muscle

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 remethylation disorders

Methylmalonic acid: a product of the mitochondria which requires disposal, elevated in combined remethylation disorders such as the cblC defect

'Good metabolic control': where homocysteine, methionine and eventually MMA levels are maintained within the desired range so as to minimise complications

Notes

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 methylation defects, please contact your consultant, clinical nurse specialist, dietician, or doctor.

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For more information:
http://ec.europa.eu/health/programme/policy/index_en.htm

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