Methylation disorders

A guide for parents, patients and families
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Introduction

You or your child have/has one of a group of diseases called methylation disorders. Currently, four methylation disorders have been described and they are all very rare.

The 4 disorders are methionine adenosyltransferase (MAT) deficiency, glycine-N-methyltransferase (GNMT) deficiency, S-adenosylhomocysteine hydrolase (SAHH) deficiency and adenosine kinase (AK) deficiency. These four disorders share some features, but they also differ from each other. This booklet describes the shared features and the specific features of individual diseases.

Initially, information about the methylation disorders may be hard to understand, especially at a time when you are worried and given lots of medical information. Please read this booklet at your leisure, and then write down any important questions that you may want to ask your specialist doctor, nurse or dietician.

What is metabolism?

Like other functions in our body, for instance, heart function or kidney function or brain function, metabolism needs to work properly to keep us healthy. Metabolism refers to the transformation of compounds into other compounds in our bodies.

Some of the compounds are derived from food and others are produced in our bodies. In diagrams, we show this transformation with arrows between the original compound and the compound that is produced (see Figure 1). Often, the reactions will only take place if they are helped by special proteins, called enzymes.

Figure 1. Metabolic reaction - transformation of compound A into compound B with the help of an enzyme.
What is a metabolic disorder? What is a metabolic disease?

When a reaction cannot take place due to lack of an enzyme, we call this a “metabolic disorder”. This leads to the accumulation of the initial compound and a lack of the compound which should have been produced. Depending on the disorder, both consequences can cause problems.

If a metabolic disorder causes problems, we call it a metabolic disease. Most metabolic disorders result from the lack of an enzyme, including all the methylation disorders described in this brochure.

What does inherited metabolic disease mean?

The formation of each enzyme depends on a gene. If there is a fault in the gene, the corresponding enzyme will not work properly. Faults in genes are called mutations.

If a metabolic disease is caused by a mutation in a gene, the disease is called an inherited metabolic disease.
Methylation defects and methionine metabolism

Proteins are made from 20 building blocks, called amino acids. One of these amino acids is called methionine. Methylation defects are disorders of methionine metabolism.

Methionine can be derived from protein in our diet or, during periods of starvation, from our body’s proteins (Figure 2). In our body, amino acids are used for the production of new proteins necessary for growth, tissue repair and many other functions.

Figure 2. Metabolism of amino acids
**Methionine metabolism** is complicated. Figure 3 presents it in a simplified way to show where the methylation defects are. Methionine is converted to S-adenosylmethionine by an enzyme called **methionine adenosyltransferase**. S-adenosylmethionine contains a methyl group (CH3), which it can transfer to other chemicals. Many reactions in our body depend on the transfer of a methyl group, so S-adenosylmethionine production is an essential process in most cells.

![Diagram of methionine metabolism]

**Figure 3.** Methionine metabolism. Purple circles depict the enzymes, whose deficiencies cause the methylation defects described in this booklet.

The transfer of methyl groups is illustrated in Figure 3 using the abbreviation CH₃. In all four methylation defects, there is something wrong with the transfer of methyl groups.
The signs and symptoms of methylation disorders are very variable. Different disorders cause different problems but, even for the same disorder, different people are affected differently. The following descriptions will not, therefore, be true for everyone with each disease. Moreover, methylation defects are very rare and doctors have very limited experience with them; this means that we do not know everything about this group of disorders.

**Methionine adenosyltransferase deficiency**

The disease seems to be harmless in most patients. When patients have had symptoms, they have generally affected the brain and have included delayed language development, learning disabilities, movement disorder such as trembling, stiffness, uncontrolled eye movements and headaches. The disease can be associated with an unusual body odour due to a very high concentration of methionine. One patient had an enlarged liver but this may not have been due to the disorder.

Symptoms may develop over time as patients get older. Individuals with a severe enzyme deficiency and very high blood methionine concentrations are at greater risk of problems, but even people with no enzyme activity can be asymptomatic.
Glycine N-methyltransferase deficiency

This disease is very rare and has only been described in five people. All five had mild biochemical abnormalities indicating liver disease and were diagnosed in childhood. Two children had an enlarged liver and one had poor weight gain. The other children were asymptomatic.

S-adenosylhomocysteine hydrolase deficiency

This disease is very rare and, so far, only ten patients have been diagnosed. Nine cases were children and one was an adult. Two sisters had a severe form of the condition and died in infancy. Both babies were bloated when they were born, probably because their liver did not make enough protein and the low protein level in the blood caused fluid to leak out. They also had severe muscle weakness, which affected their breathing, and structural abnormalities of the brain.

Though less severely affected, the other patients have also had significant problems. All had weakness and delayed developmental milestones such as sitting and walking. Some babies were sluggish, with little interest in their surroundings. Most patients had a squint. Many have had behaviour problems, such as poor attention and hyperactivity. Some patients have abnormal blood clotting, either an increased tendency to bleed or an increased risk of blood clots.

Adenosine kinase deficiency

This disease has only been diagnosed in 20 patients. Problems usually appeared soon after birth, with floppiness, jaundice and liver disease. Many patients had an unusual facial appearance with a prominent forehead and some had congenital heart disease. All patients have had delayed development and learning difficulties. Some patients have suffered from epilepsy, low blood sugar levels and deafness.

Treatment

The treatment for methylation defects depends on the disorder. In some patients, we can only treat the symptoms of the disease, not the underlying cause. Treatment of symptoms is aims to reduce the symptoms and improve the comfort and well-being of the patient.
MAT deficiency

This disease seems to be harmless in most patients; treatment is only needed in people who have the problems described in the previous section. It is thought that patients with a blood methionine concentration above 600 µmol/L are at a higher risk of developing symptoms, so they may also need treatment. In patients with high methionine levels or symptoms, treatment aims to reduce the plasma methionine concentration and to keep the S-adenosylmethionine concentration in the normal range.

The treatment includes a low protein diet, similar to a vegetarian diet. Patients should avoid or restrict meat (including fish and poultry), meat products, eggs, milk and dairy intake. This diet should be adapted to your personal needs in collaboration with your doctor and dietician. Since methionine is only found in protein, reducing the protein intake also reduces the methionine intake. Only a very small amount of natural protein is allowed in the diet; this is not sufficient to meet our daily protein requirement, so patients on the diet need supplements containing all the building blocks of protein apart from methionine. These supplements are known as protein substitutes and they come as drinks or powders.

Treatment with S-adenosylmethionine may also help, especially if the blood S-adenosylmethionine level is too low or if methionine restriction does not improve the symptoms. It is taken by mouth and can be prescribed by your doctor.

GNMT deficiency

One patient with this condition was given a low-protein, low-methionine diet. This corrected the blood levels of methionine and S-adenosylmethionine and the diet may be necessary if the blood methionine exceeds concentrations of about 600 µmol/L, judging from experience in MAT deficiency. In addition, careful monitoring is necessary, since animal studies suggest that there is a risk of liver disease in the long term.

SAHH deficiency

A low-protein diet may help some of these patients, especially if started early. It is similar to vegetarian diet. Patients should avoid or restrict meat, meat products (including), fish, poultry, eggs, milk and dairy intake. This diet should be adapted to your personal needs in collaboration with your doctor and dietician. Since methionine is only found in protein, reducing the protein intake also reduces the methionine intake. Only a very small amount of natural protein is allowed in the diet; this is not sufficient to meet our daily protein requirement, so patients on the diet need supple-
Methylation defects are genetic conditions. This means that they are 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 methylation disorders is called **autosomal recessive**. This means that everyone has two copies of the relevant gene but, in people with the disorder, both copies are faulty. The parents each have one normal copy of the gene and one faulty copy and they are called "carriers". Carriers are well and do not have any symptoms of the condition. If both parents are carriers for a methylation defect, there is a 1 in 4 (25%) chance in each pregnancy that the child will have this defect. There is also a 1 in 2 (50%) chance that the baby will be a carrier, like the parents, and a 1 in 4 (25%) chance that the baby will have inherited two normal copies of the gene.

**AK deficiency**

A low-methionine diet improved the liver disease in a number of patients but it had little effect on the neurological problems. The drug, diazoxide, is an effective treatment for low blood sugar levels. Antiepileptic therapy and multidisciplinary support may also be needed.

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

Methylation defects are genetic conditions. This means that they are 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 methylation disorders is called **autosomal recessive**. This means that everyone has two copies of the relevant gene but, in people with the disorder, both copies are faulty.

The parents each have one normal copy of the gene and one faulty copy and they are called "carriers". Carriers are well and do not have any symptoms of the condition. If both parents are carriers for a methylation defect, there is a 1 in 4 (25%) chance in each pregnancy that the child will have this defect. There is also a 1 in 2 (50%) chance that the baby will be a carrier, like the parents, and a 1 in 4 (25%) chance that the baby will have inherited two normal copies of the gene.
How does this occur?

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

At conception, it is impossible to predict which egg and sperm will join to form the baby. Each egg and each sperm will carry one copy of the gene for each methylation enzyme. If both the egg and the sperm have faulty copies then the baby will be affected by this methylation defect.
Is prenatal diagnosis available?

Prenatal diagnosis is possible for all four methylation defects, and is best done by mutation analysis. Prenatal diagnosis may not always be appropriate, however, as some of the conditions only cause mild problems; in other cases, the decision will depend on the parental attitudes and other factors. These issues should be considered carefully with an experienced genetic counsellor.

It is strongly recommended that the pregnancy is planned and discussed with the metabolic and obstetric teams in advance.

What does the future hold for my child?

All methylation disorders are lifelong conditions that require lifelong monitoring and specialist clinic visits. Treatment may be necessary, depend on which disorder your child has and its severity.

It is hard to predict the future accurately because there is limited knowledge and experience for this group of diseases. Patients with MAT deficiency should have a good outcome and a good quality of life, if monitored properly and treated when necessary. We do not expect any long-term problems in GNMT deficiency but this disease is so rare that we cannot be sure of this. The quality of life and outcome in SAHH deficiency depends on the form and severity of the disease. In the moderate and milder forms, treatment may help and these patients may have an acceptable quality of life and participate in many everyday activities. In addition, medical progress may result in further benefits for these patients. The same could be true for AK deficiency. The first reported cases of this condition were so severe that treatment seemed unlikely to help. Very recent data, however, suggest that there may be milder forms in which treatment may be more effective.
School and education

Most children with MAT deficiency and GNMT deficiency can attend a normal school. Some patients with MAT deficiency have learning difficulties, especially those with very high blood methionine concentrations.

Patients with SAHH deficiency generally need extra help at school. So far, patients with AK deficiency have been too severely affected to attend normal school.

Pregnancy

Due to the rarity of methylation disorders, we only know about pregnancies in one affected woman, who had MAT deficiency. The mother remained healthy and three healthy babies were born; the fourth embryo died at 10-11 weeks gestation but miscarriages are common at this stage so it may not have been due to the MAT deficiency. No pregnancies have been reported in the other methylation disorders.

In MAT deficiency, it is recommended that pregnancies are planned in advance with the specialist consultant. If the woman is on a low protein diet, this should be adjusted and carefully monitored before conception and throughout pregnancy. Similar care should be provided for women with SAHH deficiency. In addition, in this disease blood clotting should be checked and, if necessary, treatment started.
Travel

Having a methylation defect should not generally prevent someone from travelling but it is wise to take sensible precautions if planning an extended trip or if going abroad.

If the patient is on a special diet, he/she will need to take enough supplies to last the duration of the trip. The same is true for drugs. Other precautions may be needed, depending on the patient’s symptoms (e.g. epilepsy).

It is recommended that the patient or his family carries some information regarding the nature of his/her illness as methylation defects are rare conditions and many doctors will not have encountered them before. This information can be provided by your clinical team. For longer periods abroad, your medical team may be able to suggest a local doctor who 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
Methionine: an amino acid that is converted in the body to homocysteine
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:

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