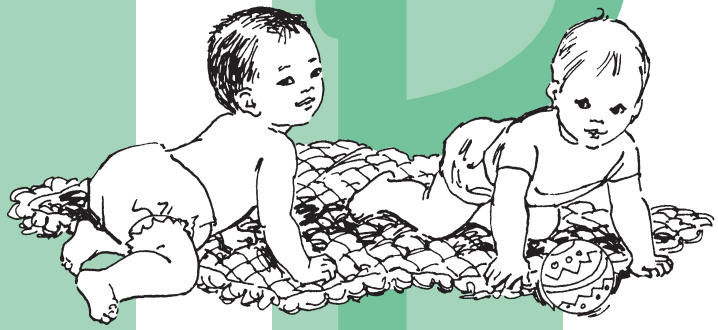
Parents' Guide to PA

Propionic Acidemia



California Department of Health Services

Newborn Screening Program
Genetic Disease Branch
www.dhs.ca.gov/gdb

June 2005

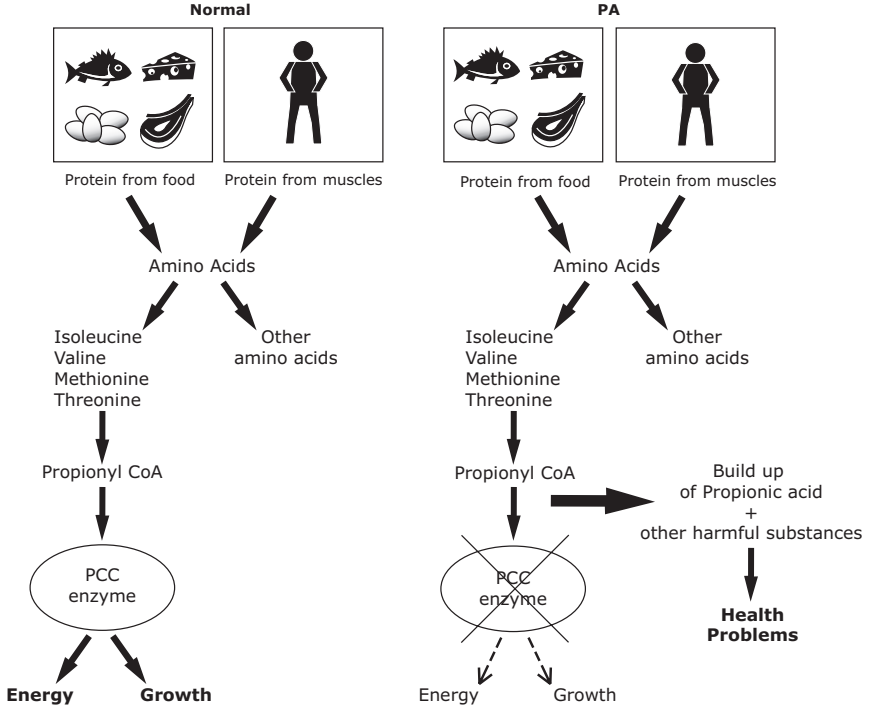
Table of Contents

*Underlined words in booklet are defined in the Glossary

The information in this booklet is general and is not meant to be specific to each child with Propionic Acidemia (PA). Certain treatments may be recommended for some children but not others. Children with PA should be followed by a physician specializing in metabolic diseases (metabolic specialist) in addition to their primary doctor. For a list of metabolic centers, see page 20 or visit our website at www.dhs.ca.gov/gdb.

What is PA?

PA stands for “propionic acidemia.” It is one type of organic acid disorder. People with these disorders have problems breaking down and using certain amino acids from the food they eat.



What causes PA?

In order for the body to use protein from the food we eat, it is broken down into smaller parts called amino acids. Special enzymes then make changes to the amino acids so the body can use them.

PA occurs when an enzyme called “propionyl CoA carboxylase” (PCC) is either missing or not working properly. This enzyme’s job is to change certain amino acids so the body can use them. When this enzyme is not working, substances called glycine and propionic acid, along with other harmful substances, build up in the blood and cause problems.

The four amino acids that cannot be used correctly are isoleucine, valine, methionine, and threonine. These amino acids are found in all foods that contain protein. Large amounts are found in meat, eggs, milk and other dairy products. Smaller amounts are found in flour, cereal, and some vegetables and fruits.

What causes the PCC enzyme to be missing or not working correctly?

Genes tell the body to make various enzymes. People with PA have a pair of genes that do not work correctly. Because of these gene changes, the PCC enzyme does not work properly or is not made at all.

If PA is not treated, what problems occur?

Each child with PA is likely to have somewhat different effects. Many babies with PA start having symptoms in the first few days of life. Others have their first symptoms sometime in infancy.

PA causes episodes of illness called metabolic crises. Some of the first symptoms of a metabolic crisis are:

- poor appetite
- vomiting
- extreme sleepiness or lack of energy
- low muscle tone (floppy muscles and joints)

Common lab findings are:

- ketones in the urine
- high levels of acidic substances in the blood, called metabolic acidosis
- high blood ammonia levels
- high blood levels of glycine
- high levels of certain organic acids
- low platelets
- low white blood cells

If a metabolic crisis is not treated, a child with PA can develop:

- breathing problems
- seizures
- swelling of the brain
- stroke
- coma, sometimes leading to death

Between episodes of metabolic crisis, children with PA are often healthy.

A metabolic crisis can be triggered by:

- eating large amounts of protein
- illness or infection
- going too long without food
- stressful events such as surgery

Long-term effects are seen in some children with PA. These can include:

- learning disabilities or mental retardation
- delays in walking and motor skills
- abnormal involuntary movements (dystonia or choreoathetosis)
- rigid muscle tone, called spasticity
- poor growth with short stature
- seizures
- osteoporosis
- inflammation of the pancreas, called pancreatitis
- skin rashes

Without treatment, brain damage can occur. This can result in mental retardation. If not treated, many babies with PA die within the first year of life.

A small number of people with PA never have symptoms and are only found after a brother or sister is diagnosed.

What happens when PA is treated?

Babies who have prompt and ongoing treatment before they have a metabolic crisis may have normal growth and development. In general, the earlier treatment is started, the better the outcome.

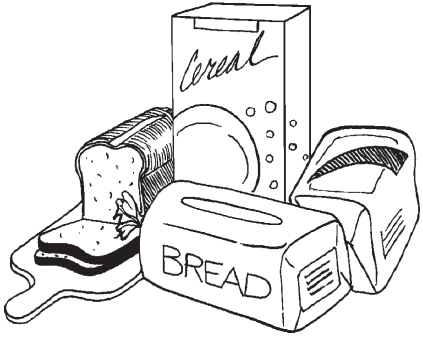
Even with treatment, some children have life-long learning problems or mental retardation. Seizures or problems with involuntary movements also occur in some children, despite treatment. Children with PA often have more infections than usual. These need to be treated promptly to avoid a metabolic crisis.

What is the treatment for PA?

Your baby's primary doctor will work with a metabolic specialist and a dietician to care for your child.

Prompt treatment is needed to prevent mental retardation and serious medical problems. Most children need to be on a low-protein diet and drink a special medical formula. You should start the diet and formula as soon as you know your child has PA.

The following are treatments often recommended for children with PA:



1. Low-protein diet, medical foods and medical formula

A food plan low in the amino acids leucine, valine, methionine, and threonine, with limited amounts of protein is often recommended. Most food in the diet will be carbohydrates (bread, cereal, pasta, fruit, vegetables, etc.). Carbohydrates give the body many types of sugar that can be used as energy. Eating a diet high in carbohydrates and low in protein can help prevent metabolic crises.

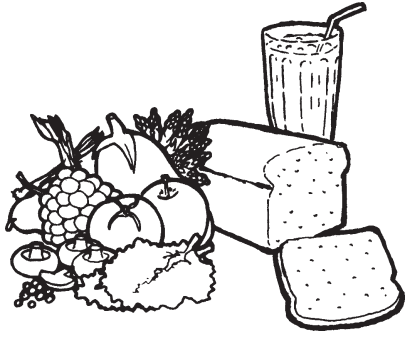
Foods high in protein that may need to be avoided or limited include:

- milk and dairy products
- meat and poultry
- fish
- eggs
- dried beans and legumes
- nuts and peanut butter

Many vegetables and fruits have only small amounts of protein and can be eaten in carefully measured amounts. Do not remove all protein from the diet. Children with PA need a certain amount of protein to grow properly.

Your dietician will create a food plan that contains the right amount of protein, nutrients, and energy to keep your child healthy. Your child will need to be on a special food plan throughout his or her life.

In addition to a low-protein diet, your child may be given a special medical formula. This formula contains the correct amount of protein and nutrients needed for normal growth and development. Your metabolic specialist and dietician will tell you what type of formula is best and how much to use.



There are also medical foods such as special low protein flours, pastas, and rice that are made especially for people with organic acid disorders. Your dietician will tell you how to use these foods as part of your child's diet.

2. Avoid going a long time without food

Babies and young children with PA need to eat often to avoid a metabolic crisis. Most children should not go without food for more than 4 to 6 hours. Some children may need to eat even more often than this. It is important that babies be fed during the night. You may need to wake them up if they do not wake up on their own.

You may be told to give your child a starchy snack before bed and another during the night. He or she may need another snack first thing in the morning. Raw cornstarch mixed with water, milk, or other drink is a good source of long-lasting energy. This is sometimes suggested for children older than one year of age. Your dietician can give you ideas for suitable snacks.

3. Medication

Children with PA may benefit by taking L-carnitine. This is a safe and natural substance that helps the body make energy. It also helps get rid of harmful wastes. L-carnitine is part of the usual treatment for PA. Your doctor will tell you how much your child needs.

Certain antibiotics, taken by mouth, can help reduce the amount of propionic acid in the intestines. Your doctor will decide if your child needs antibiotics and, if so, what type.

Some children may be given biotin supplements by mouth. Biotin is a type of B vitamin that helps the body make energy from food.

Biotin has not been proven to help in PA. But, your doctor may talk with you about trying this supplement to see if it is of benefit to your child.

Children who are having symptoms of a metabolic crisis should be treated in the hospital. During a metabolic crisis, your child may be given medications such as bicarbonate by intravenous (IV) to help reduce the acid levels in the blood. Glucose is often given by IV to prevent the breakdown of protein and fat stored in the body.

Do not use any medication or supplement without first checking with your doctor or metabolic specialist.

4. Regular urine and blood tests

Your child will have periodic urine tests to check the level of ketones. These can be done at home or at the doctor's office. Ketones are substances formed when body fat is broken down for energy. This can happen after going without food for long periods of time, as the result of an illness, or during periods of heavy

exercise. Ketones in the urine may signal the start of a metabolic crisis.

Your child will have regular blood tests to measure the levels of amino acids. Urine tests may also be done. Your child's diet and medication may need to be adjusted based on the results of these tests.

5. Call your doctor immediately if your child has signs of illness

In children with PA, even minor illness can lead to a metabolic crisis. In order to prevent problems, call your doctor right away when your child has any of the following symptoms:

- loss of appetite
- vomiting
- diarrhea
- infection or illness
- fever

Children with PA need to eat more starchy foods and drink more fluids when they are ill – even if they aren't hungry – or they could have a metabolic crisis. In addition, they should avoid eating protein during any illness.

Many children with PA need to be treated in the hospital during illness to avoid serious health problems.

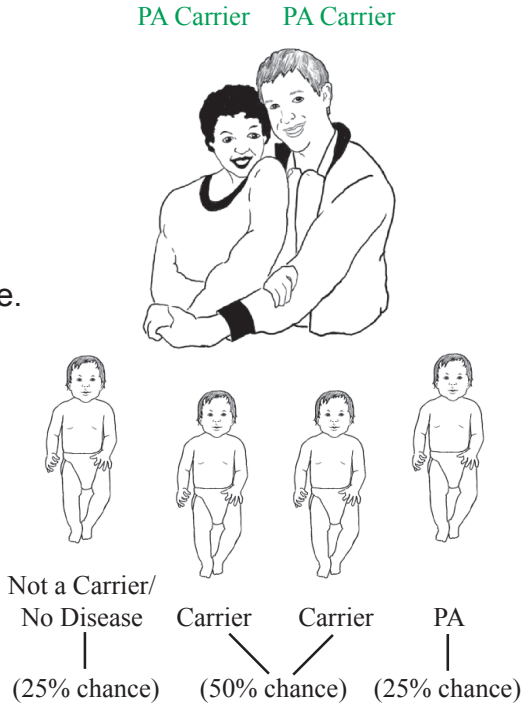
How is PA inherited?

PA affects both boys and girls equally.

Everyone has a pair of genes that make the PCC enzyme. In children with PA, neither of these genes works correctly. These children inherit one non-working gene for the condition from each parent. This is called autosomal recessive inheritance.

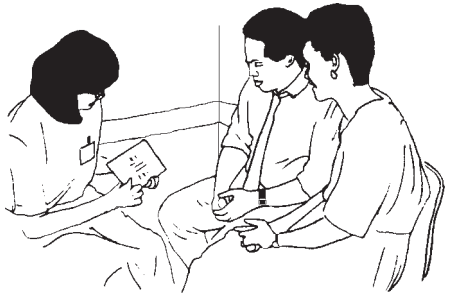
Parents of children with PA rarely have the disorder. Instead, each parent has a single non-working gene for PA. They are called carriers. Carriers are not affected because their other gene of this pair is working correctly.

When both parents are carriers, there is a 25% chance in each pregnancy for the child to have two working genes. This means the child is not a carrier and does not have the disease. There is a 50% chance for the child to be a carrier, just like the parents. There is a 25% chance for the child to have PA.



Chances apply to each pregnancy

Genetic counseling is available to families who have children with PA. Genetic counselors can answer your questions about how PA is inherited, options during future pregnancies, and how to test other family members. Other family members can also ask about genetic counseling and testing for PA.



Is genetic testing available?

Genetic testing for PA may be possible. Genetic testing, also called DNA testing, looks for changes in the pair of genes that cause PA. Talk with your genetic counselor or metabolic specialist if you have questions about DNA testing.

DNA testing may not be necessary to diagnose your child. However, if it is available, it can be helpful for carrier testing or prenatal diagnosis.

What other testing is available?

Special tests on blood, urine or skin samples can be done to confirm PA. Talk to your metabolic specialist or genetic counselor if you have questions about testing for PA.

Can you test during pregnancy?

If both gene changes are known in your child with PA, DNA testing can be done during future pregnancies to determine if the sibling also has PA. The sample needed for this test is obtained by either CVS or amniocentesis. PA can also be found through an enzyme test using cells from the fetus. The sample needed for this test is obtained by amniocentesis.

Parents may either choose to have testing during pregnancy or wait until birth to have the baby tested. A genetic counselor can talk to you about your choices and answer questions about prenatal testing or testing your baby after birth.

Can other members of the family have PA or be carriers?

Older brothers and sisters of a baby with PA who are healthy and growing normally are unlikely to have the condition. However, finding out if other children in the family have this condition may be important because treatment can prevent serious health problems. Ask your metabolic specialist or genetic counselor whether your other children should be tested.

Brothers and sisters who do not have PA still have a chance to be carriers like their parents. Carriers do not have the disorder and will never develop it.

Each of the parents' brothers and sisters has a chance to be a PA carrier. It is important for other family members to be told that they could be carriers. There is a small chance they are also at risk to have children with PA.

When both parents are known PA carriers or have had a baby with PA, subsequent newborns should have special diagnostic testing in addition to the newborn screen to test for PA.

How many people have PA?

About one in every 100,000 babies in the United States is born with PA. PA occurs in all ethnic groups around the world. It happens more often in the Arab population of Saudi Arabia. About one in 2000 to one in 5000 people of Saudi Arabian ancestry has PA.

Does PA go by any other names?

PA is sometimes also called:

- Propionyl-CoA carboxylase deficiency
- PCC deficiency
- Ketotic glycinemia
- Ketotic hyperglycinemia

RESOURCES

Propionic Acidemia Foundation
1963 McCraren
Highland Park, IL 60035
(847) 579-1824
www.pafoundation.com

Organic Acidemia Association
13210 35th Avenue North
Plymouth, MN 55441
(763) 559-1797
www.oaanews.org

Children Living with Inherited Metabolic Disorders
CLIMB Building
176 Nantwich Road
Crewe, CW2 6BG
United Kingdom
www.climb.org.uk

Save Babies Through Screening Foundation
4 Manor View Circle
Malvern, PA 19355-1622
(888) 454-3383
www.savebabies.org

Genetic Alliance
4301 Connecticut Ave. NW, Suite 404
Washington, DC 20008-2369
(202) 966-5557
www.geneticalliance.org

METABOLIC CENTERS

Cedars-Sinai Medical Center
(310) 423-9914

Children's Hospital Central California
(559) 353-6400

Children's Hospital & Research Center at Oakland
(510) 428-3550

Children's Hospital of Los Angeles
(323) 660-2450

Children's Hospital of Orange County
(714) 532-8852

Children's Hospital & Health Center
(619) 543-7800

Harbor/UCLA Medical Center
(310) 222-3756

Kaiser Permanente Medical Center, No. Cal.
(510) 752-7703

Kaiser Permanente Medical Center, So. Cal.
(323) 783-6970

Los Angeles County/ USC Medical Center
(323) 226-3816

Lucile Salter Packard Children's Hospital at Stanford
(650) 723-6858

Sutter Medical Center
(916) 733-6023

UC Davis Medical Center
(916) 734-3112

UC San Francisco Medical Center
(415) 476-2757

UC Los Angeles Medical Center
(310) 206-6581

UC Irvine Medical Center
(714) 456-8513

GLOSSARY

Amniocentesis - Test done during pregnancy (usually between 16 and 20 weeks). A needle is used to remove a small sample of fluid from the sac around the fetus. The sample can be used to test for certain genetic disorders in the fetus.

Autosomal recessive - Autosomal recessive conditions affect both boys and girls equally. How autosomal recessive inheritance works: Everyone has a pair of genes responsible for making each enzyme in the body. A person with a metabolic disorder has one enzyme that is either missing or not working properly. The problem is caused by a pair of "recessive" genes that are not working correctly. They do not make the needed enzyme. A person has to have two non-working "recessive" genes in order to have an autosomal recessive metabolic disorder. A person with an autosomal recessive disorder inherits one non-working gene from their mother and the other from their father.

Bicarbonate - A substance that lowers the amount of acid in the blood. It is some times used as part of the treatment for children with certain organic acid disorders.

Carrier - A person who has a gene mutation in one of their genes that cause a disease, but does not have any symptoms of the disease themself. The mutation

is often recessive, which means that both copies of the gene have to be mutated in order for disease symptoms to develop. Carriers are able to pass the mutation onto their children and therefore have an increased chance of having a child with the disease.

CVS - Chorionic Villus Sampling (CVS) is a special test done during early pregnancy (usually between 10 and 12 weeks). A small sample of the placenta is removed for testing. This sample can be used to test for certain genetic disorders in the fetus.

DNA - Deoxyribonucleic acid (DNA) is a molecule that makes up chromosomes. It is composed of four units (called bases) that are designated A, T, G, and C. The sequence of the bases spell out instructions for making all of the proteins in an organism. The instructions set for each individual protein is a gene. A change in one of the DNA letters making up a gene is a mutation. In some cases, these mutations can alter the protein instructions and lead to disease. Each individual passes their chromosomes on to their children, and therefore pass down the DNA instructions. It is these instructions that cause certain traits, such as eye or hair color, to be inherited.

Enzyme - A molecule that helps chemical reactions take place. For example, enzymes in the stomach speed up the process of breaking down food. Each enzyme can participate in many chemical reactions without changing or being used up.

Gene - A segment of DNA that contains the instructions to make a specific protein (or part of a protein). Genes are contained on chromosomes. Chromosomes, and the genes on those chromosomes, are passed on from parent to child. Errors in the DNA that make up a gene are called mutations and can lead to diseases.

Genetic Counseling - Genetic counseling gives patients and their families education and information about genetic-related conditions and helps them make informed decisions. It is often provided by Genetic Counselors or Medical Geneticists who have special training in inherited disorders.

Glucose - A type of sugar made from the carbohydrates in food. Glucose is found in the blood. It is the main source of energy for the body and brain.

Metabolic Crisis - A serious health condition caused by low blood sugar and the build-up of toxic substances in the blood. Symptoms of a metabolic crisis are: poor appetite, nausea, vomiting, diarrhea, extreme sleepiness, irritable mood and behavior changes. If not treated, breathing problems, seizures, coma, and sometimes even death can occur. Metabolic crises happen more often in people with certain metabolic disorders (some fatty acid oxidation disorders, amino acid disorders, and organic acid disorders). They are often triggered by things like illness or infection, going without food for a long time, and, in some cases, heavy exercise.

Osteoporosis - A condition that causes the bones to become thinner over time. People with this condition have a higher chance for bone fractures.

Seizure - Also called “convulsions” or “fits.” During a seizure, a person loses consciousness and control of their muscles. It may also cause involuntary movements. Seizures can happen for many reasons. Some causes are metabolic disorders, a metabolic crisis, brain injury, and infection.

Stroke - When the blood or oxygen supply to part of the brain is stopped. It can be caused by a blood clot or a leak in a blood vessel. It may cause loss of speech, language, and the ability to move certain body parts. If severe, it can cause death.

This booklet has been adapted from the materials developed by STAR-G Project – a multi-state collaborative project including representatives from California DHS, Newborn Screening Program, and funded by a federal grant from the MCH Bureau, Project #1 H46 MC 00189-02.

Acknowledgements

We would like to thank the following people for their help in reviewing and providing input into this booklet:

- Metabolic Specialists and Dieticians at California Children's Services (CCS) Approved Metabolic Centers
- California Newborn Screening Area Service Center staff
- Parents of children with PA