

PROTOCOL FOR NEWBORN SCREENING RESULT

Elevated C3 acylcarnitine (propionylcarnitine); possible propionic acidemia (PA) or methylmalonic acidemia (MMA).

First Newborn screening result

C3 markedly elevated, >12 $\mu\text{mol/L}$ probable PA or MMA

PA (propionic acidemia) and MMA (methylmalonic acidemia) are inborn errors of organic acid metabolism in which the organic acids derived from the amino acids isoleucine, valine, threonine and methionine and odd chain fatty acids cannot be fully metabolised to succinyl-CoA (see diagram below). The organic acid intermediates that accumulate are toxic. The major initial feature is metabolic acidosis.



History and examination

The infant and parent(s) must be seen within the next day or two following notification from the newborn screening program. A METABOLIC PHYSICIAN MUST BE CONSULTED.

History

The infant may have a normal history. The majority of patients, however, develop symptoms in the first days or weeks of life. Poor feeding and vomiting can progress rapidly to coma and death. Seizures occur in about 30% of affected infants. Since PA and MMA are both autosomal recessive genetic disorders, there is a 25% chance that sibs of the identified infant may also have PA or MMA. A family history of other children in the family becoming seriously ill or having developmental delay is highly significant.

Examination

The infant may appear entirely healthy and well. If ill, the neonatal signs are tachypnea, hypotonia, lethargy, dehydration and hypoglycemia. **ANY** signs of illness must be treated as a medical emergency and treated immediately.

Go to Acute illness protocol, PA or MMA.

If the child appears well it is still essential to refer to the metabolic center to ensure that the child and family receive the necessary treatment and guidance to prevent morbidity. Contact the metabolic physician for markedly elevated C3

ENSURE THAT THE REPEAT NEWBORN SCREENING SAMPLE IS SENT TO THE NEWBORN SCREENING LABORATORY AND THE RESULT OBTAINED ASAP

(Go to [NNSGRC](#) for the state labs)

[Discussion with parents for markedly elevated C3](#)

[Contact metabolic physician for markedly elevated C3](#)

Your local metabolic physician can be found via [metabolic physicians and specialists](#)

The metabolic physician's role

- Provides you with information on PA and MMA.
- Discusses, in further detail, the meaning of the test result with the family.
- Starts appropriate [treatment](#).
- Provides supportive counseling for the family.
- Undertakes [definitive investigations](#) .
- Provides genetic / prenatal counseling.
- Hospitalizes, if necessary, in a metabolic unit for acute illnesses. These infants can not be managed conservatively when they become ill. The threshold should be very low for hospitalization and very close metabolic monitoring by a metabolic physician.

Return to [discussion with parents for markedly elevated C3](#)

Discussion with parents for markedly elevated C3

Response to a reported newborn screening result must be undertaken in two parts:

- Initial contact with the family, often by phone, to inform them of the newborn screening result.
- Meeting with the family at the office.

Initial communication

Many parents want to know what the result is testing positive for and are reassured if their doctor has knowledge of PA and MMA or has taken the time to find out about the condition when informing the family (see **commonly asked questions**).

Highly elevated C3 acylcarnitine (propionylcarnitine) levels of $>12 \mu\text{mol/L}$ usually means that the infant has PA or MMA.

PA and MMA are related diseases in which the amino acids leucine, valine, methionine and threonine cannot be fully metabolized to succinyl-CoA. PA and MMA are the penultimate and ultimate steps respectively in the metabolism of these amino acids to succinyl-CoA (see diagram of pathway). TREATMENT is available to help with both these conditions. The mainstay of treatment is prevention and early aggressive treatment for illness. It is essential that parents arrange to see a metabolic doctor as soon as possible.

In the office

Many parents do not understand newborn screening or the need to treat their apparently healthy baby.

Parental anxiety will be high and it is important to reassure them that

- Treatment is available
- Failure to treat a baby with PA or MMA may result in life threatening illness that could produce seizures, dystonia, chorea or mental retardation. Other known complications of propionic acidemia include pancreatitis, leukopenia and thrombocytopenia, heart failure and sudden death.

Treatment for PA or MMA is based on maintaining energy levels and avoiding life threatening energy deficit. When this happens, the metabolic doctor must be contacted and involved to ensure that all the necessary metabolic tests and measures are carried out.

Further counseling, treatment and a more detailed assessment and testing of the infant is required; therefore **contact metabolic physician for markedly elevated C3**

Commonly asked questions

1. What is PA or MMA?

PA is also known as propionic acidemia. MMA is also known as methylmalonic acidemia. They are organic acid disorders and represent defects in the metabolism of certain essential amino acids. The inability to completely metabolise these amino acids leads to a build up of toxic intermediate chemicals. This is often exacerbated at times when the body is stressed (e.g. fasting, operations or infections). During these times the body breaks down its own proteins to supply needed energy and as a result, the amino acids are metabolized into the toxic intermediates.

2. How and when will we know if my baby has PA or MMA?

If your baby's newborn screening result showed a markedly elevated C3 levels, he or she probably has PA or MMA. The newborn screening test will be repeated and additional tests will be undertaken to help determine whether or not your baby has PA or MMA. Typically, the results of these tests take up to 4 days to come back. Depending on the test results, additional testing can take a variable amount of time to confirm the diagnosis. In a very small minority of cases it can be difficult to determine whether or not a child is affected.

3. How did my baby get this?

PA and MMA are autosomal recessive genetic disorders. This means that your baby has two abnormal genes, one from the mother and one from the father. Having only one mutated gene (a carrier) does not affect a person at all.

4. What does it mean for my child?

If your baby has PA or MMA, he or she will have to have a special protein restricted diet. Most children with these conditions also take carnitine, a mild supplemental medicine. If your child becomes ill, it may well be necessary early in the illness (i.e. when it might be considered mild), to further restrict the protein intake for a short period of time or even to provide extra energy in the form of glucose through addition to food or, if necessary, by intravenous infusion. By treating your baby this way it is possible to generally prevent the worst effects of these conditions. However, babies and children with PA or MMA are at risk from serious effects such as mental retardation, loss of control of movement or even death if allowed to get sick throughout childhood. Therefore, it is important to maintain vigilance, consider every illness seriously and hospitalize for specialized treatment early. Some children, despite the best treatment and care possible, will still have some delay though this will be significantly less than if your child is not treated as described above. Children with PA also tend to have feeding difficulties up to the early school years when this problem typically abates.

5. What is the treatment? Does it work? Is the diet difficult to do/expensive?

PA or MMA is primarily treated by a protein restricted diet with supplemental amino acid formula. The special formula which will keep your child well is typically ordered through your metabolic clinic where the metabolic nutritionist will ensure that you are confident in preparing it. The formula can be expensive; however, your metabolic clinic will assist you in obtaining it through your health care provider or state agency.

6. What about my other children/future children?

As PA and MMA are inherited conditions it is essential to have your other children tested. Children from the same father and mother as the affected infant have a 1 in 4 (25%) chance of having the same condition. Your other children can appear healthy and still

have the disease. If they have PA or MMA, successfully having weathered illnesses in the past is no guarantee that an illness in the future will not have serious consequences. Since there is a risk for having a future child with PA or MMA it is important to let your obstetrician and pediatrician know that you have a child with PA or MMA if you are planning future pregnancies so that they may discuss the options with you and prepare accordingly.

Definitive Investigations

1. Quantitative urine organic acids

In symptomatic patients with PA there is an increase in propionyl-CoA metabolites. (This is also the case in MMA when secondary inhibition of propionyl-CoA carboxylase occurs). These elevations, particularly in PA, include 3-hydroxypropionate and methylcitrate. Also elevated to a lesser degree are 3-hydroxyisovaleric acid, tiglic acid, tiglylglycine, propionylglycine, 2-methyl 3-hydroxybutyrate and 3-hydroxybutyrate. Methylmalonic acid is highly elevated in MMA, whereas it is absent in PA.

The presence of ketones, especially in large quantities is highly suggestive of PA or MMA, particularly in the neonatal period when ketones are typically absent.

2. Plasma acylcarnitines

The profile of patients with PA or MMA is characterized by increased propionylcarnitine (C3) as determined by tandem mass spectrometry.

3. Acute laboratory tests

Acute management labs should take priority (blood glucose, plasma ammonia, blood gases, electrolytes and urinalysis for ketones). Diagnostic and follow up management labs during acute illness include urinalysis for ketones, urine for organic acids, plasma acylcarnitines and plasma amino acids. See [Acute illness protocol, PA or MMA.](#)

4. Enzyme assay. [Go to genetests](#)

Propionyl-CoA carboxylase and methylmalonyl-CoA mutase enzymatic activity can be measured in cultured fibroblast cells (e.g. from a skin biopsy).

5. Molecular testing

Genotyping is available for both PA and MMA. [Go to genetests](#)

Treatment

Diet

The mainstay in treatment of PA or MMA beyond the immediate acute neonatal illness is specific dietary treatment with restriction of valine, isoleucine, methionine and threonine. Often supplemental amino acids, necessary to avoid general amino acid deficiency states, is provided through night-time gastric feeding.

Constipation (applies to PA only)

Constipation leads to an increase in gut floral production of propionic acid. It is therefore important to ensure that children with PA do not become constipated. It may also be necessary at times to provide antibiotic clearance of the gut bacteria using neomycin or metronidazole. Protocols for this are generally instituted by the metabolic physician caring for the child with PA.

Carnitine

Carnitine at a dose of 100mg/kg/day appears to help by converting the toxic propionyl-CoA to propionylcarnitine and releasing CoA intracellularly for other metabolic needs. Carnitine is also useful in both PA and MMA to treat hypocarnitinemia.

B12 (applies to MMA only)

Mild cases of MMA may be helped by B12. A trial of B12 under careful metabolic control may be warranted and, where successful, may allow a less stringent protein restricted diet.

Acute illness treatment

Any time the child is sick an evaluation should be made and the child's metabolic physician contacted. Protein intake must initially be restricted or stopped entirely. Prophylactic intravenous 10% glucose should be given if the child is unable to eat or is vomiting or physiologically stressed, even mildly, to prevent catabolism and consequent release of toxic amino acids. The threshold for aggressive treatment should be very low. Constipation should be treated aggressively.

Note: it is important not to prolong protein free diet as this will quickly lead to a catabolic state. The metabolic physician should be the doctor determining daily protein allowance. All patients should be provided with an up to date personalized "emergency" letter for an ER or other doctors who are probably not familiar with PA or MMA. This letter should include management issues and emphasize the importance of preventive measures (*e.g.*, IV 10% glucose regardless of "normal" laboratory results and the telephone numbers of the patient's metabolic specialist who needs to be contacted to discuss management). See

[Acute illness protocol](#).