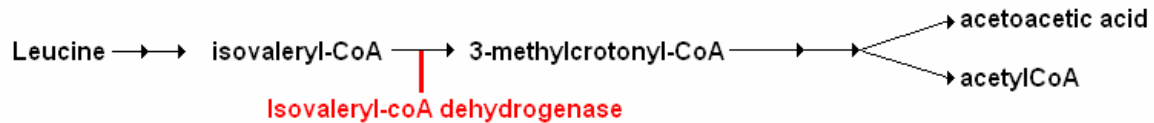


C5 markedly elevated, probable IVA

IVA (isovaleric acidemia) is an inborn error of organic acid metabolism in which the organic acids derived from the amino acid leucine cannot be fully catabolized because there is a block at the third stage in the pathway from isovaleryl-CoA to 3-methylcrotonyl-CoA (see diagram below). The organic acid intermediates that accumulate (isovaleric acid, 3-OH-isovaleric acid) are toxic. The major initial feature is metabolic acidosis and a “sweaty foot” odor.



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. IVA may present after infancy or in the first 14 days of life. The first symptoms include refusal to feed, vomiting, drowsiness and seizures.

Examination

The infant may appear entirely healthy and well. Weight loss or poor weight gain, as well as signs of dehydration, lethargy, hypothermia, hepatomegaly, raised intracranial pressure or other neurological features and a foul “sweaty feet” odor may be present. ANY signs of illness must be treated as a medical emergency and treated immediately.

Go to Acute illness protocol, IVA.

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 C5

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 C5

Contact metabolic physician for markedly elevated C5

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

The metabolic physician's role

- Provides you with information on IVA.
- 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 cannot 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 C5](#)

Discussion with parents for markedly elevated C5

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 IVA or has taken the time to find out about the condition when informing the family (see [commonly asked questions](#)).

Highly elevated C5 acylcarnitine (isovalerylcarnitine or 2-methylbutyrylcarnitine) levels of $> 4 \mu\text{mol/L}$ usually means that the infant has IVA (isovaleric acidemia) or, much more rarely, 2-methylbutyryl-CoA dehydrogenase deficiency.

IVA is a disease in which the amino acid leucine cannot be fully metabolized (see diagram of pathway). TREATMENT is available for this condition. The mainstay of treatment is prevention of illness with early treatment. It is essential that parents arrange to see a metabolic doctor as soon as possible.

2-methylbutyryl-CoA dehydrogenase deficiency is a defect in the metabolism of the amino acid isoleucine and has only been reported in a handful of cases. The primary problems reported for these children have been neurological.

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 IVA may result in mental retardation or life threatening illness that includes seizures, spasticity, coma and death.
-

Treatment for IVA 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 C5](#)

Commonly asked questions

1. What is IVA?

IVA is also known as isovaleric acidemia and is an organic acid disorder caused by a defect in the metabolism of a specific essential amino acid, leucine. The inability to completely metabolize this amino acid leads to a build up of toxic intermediate chemicals. This is often exacerbated 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 IVA?

If your baby's newborn screening result showed a markedly elevated C5 levels, he or she probably has IVA. The newborn screening test will be repeated and additional tests will be undertaken to help determine whether or not your baby has IVA. 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?

IVA is an autosomal recessive genetic disorder. This means that your baby has two abnormal mutated 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 IVA, he or she will have to have a special protein restricted diet. Most children with this condition also take glycine and 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 IVA 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.

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

IVA is primarily treated by a protein-restricted diet and special formula composed of amino acids. 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 IVA is an inherited condition 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 disorder. If they have IVA, 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 IVA it is important to let your obstetrician and pediatrician know that you have a child with IVA 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 patients with IVA there is an increase in the isovaleryl-CoA metabolites hydroxyisovalerate and isovalerylglycine.

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

2. Plasma acylcarnitines

The profile of patients with IVA is characterized by increased isovalerylcarnitine (C5) as determined by tandem mass spectrometry.

3. Acute laboratory tests

Acute management labs should take priority (blood glucose, plasma ammonia, blood gases, electrolytes, LFTs, PT, PTT, carnitine 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, IVA.](#)

4. Enzyme assay

Isovaleryl-CoA dehydrogenase enzymatic activity can be measured in cultured fibroblast cells (e.g. from a skin biopsy). [Go to genetests](#)

5. Molecular testing

Specific mutations have been identified for IVA in the isovaleryl-CoA dehydrogenase (IVD) gene. [Go to genetests](#) to determine if molecular testing is being offered.

Treatment

Diet

The mainstay in treatment of IVA beyond the immediate acute neonatal illness is specific dietary treatment with restriction of leucine. Often supplemental amino acids, including a minimal amount of leucine, is necessary to avoid amino acid deficiency states. This may be provided, in some cases, through nighttime gastric feeding.

Carnitine & Glycine

Carnitine and glycine interact with isovaleric acid to form nontoxic readily excreted products of isovalerylcarnitine and isovalerylglycine respectively. Carnitine is given at a dose of 100 mg/kg/day in two divided doses per day and glycine at 250 mg/kg in three divided doses per day.

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 a 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 IVA. 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](#).