

FATTY ACID DISORDERS

FATTY ACID OXIDATION DISORDERS

Fatty acid oxidation disorders are a group of inherited metabolic conditions, each associated with a deficiency of an enzyme which is needed for the conversion of fatty acids to energy. Life-threatening situations can occur during episodes of fasting or illness in children with untreated fatty acid oxidation disorders.

Fatty Acid Oxidation Disorders Screened in Kansas

The newborn screening program in the State of Kansas is designed to screen for five different fatty acid disorders. These disorders include:

- Medium Chain acyl-CoA Dehydrogenase Deficiency (MCADD)
- Long Chain 3-OH acyl-CoA Dehydrogenase Deficiency (LCHADD)
- Very Long Chain acyl-CoA Dehydrogenase Deficiency (VLCADD)
- Tri-Functional Protein Deficiency (TFP)
- Carnitine Uptake Defect (CUD)

Clinical Features in Children with Untreated Fatty Acid Oxidation Disorders

In untreated fatty acid oxidation disorders, fasting and illness can elicit a metabolic crisis. Symptoms may include vomiting, diarrhea, lethargy, seizures, coma and difficulty breathing. Awareness of how to diagnose and treat these disorders is vital because during a metabolic crisis, an undiagnosed individual may experience excessive buildup of fat in the liver, heart and kidneys, along with some brain swelling—all of which can lead to death.

Laboratory Screening Tests

Fatty acid oxidation disorders are screened using a tandem mass spectrophotometer (MS/MS). MS/MS technology tests for certain analytes which are present in the baby's blood sample. If a particular analyte is abnormal, the MS/MS instrument will flag that sample to indicate the abnormal result. The instrument will interpret positive samples as either low risk (LR), moderate risk (MR) or high risk (HR). Often, secondary markers are taken into consideration when determining the risk level. These secondary markers may be actual analyte levels or the ratio of two analytes. All results are reviewed by trained technicians prior to being reported.

The cutoffs values for MS/MS analytes are reviewed periodically, as more data is collected. Cutoffs are adjusted as needed, which can reduce false positive and false negative results.

Confirmatory Testing

Infants with low risk results on the initial newborn screening need to have the screening promptly repeated. If the initial results are high risk, consultation with a metabolic specialist and diagnostic testing should be promptly scheduled.

Treatment

Treatment for fatty acid oxidative disorders includes avoidance of fasting as well as prolonged exercise. Several of these disorders require a special diet and nutritional supplements. CUD is treated with carnitine supplements.

Screening Practice Considerations

Early specimen collection (after first 24 hours of age) may enhance the detection of these disorders, as acylcarnitine levels may decrease with infant age, even in affected infants. For this reason, it is essential that a repeat test be collected as soon as possible. False positive and false negative results are possible with this screening.

If the baby was transfused, repeat the screening on day 4 after transfusion.

Medical Consultant

A medical consultant is available to provide consultation for the follow-up, evaluation, and long-term management of children with fatty acid oxidative disorders. Please contact:

Dr. Majed Dasouki
KU Medical Center
Kansas City, KS
Office 913-588-6326

It is strongly recommended that prior to repeating the newborn screen practitioners should confer with the consultant. The consultant may recommend repeating the state newborn screen, or may suggest labs to draw and analyze in a practitioner's local lab. The consultant may wish to see the newborn in the office and do the lab work and assessment there. Whatever the case, we want to prevent unnecessary lab draws or inappropriate testing on these infants. In summary, please contact the consultant prior to drawing the repeat blood work.

Overview of Follow-up Procedure

Abnormal Newborn Screening for Fatty Acid Oxidative Disorders

- 1) Newborn screening follow-up team reviews the laboratory reports that are faxed overnight from the lab or records the information provided per telephone call from the laboratory on a white phone information sheet.
- 2) If the result is considered **normal**:
 - a) Follow-up team does not receive results.
 - b) Lab will fax or mail results to doctor listed on NBS card.
- 3) If the result is **Low Risk (LR)**:
 - a) Lab will contact follow-up team via phone and/or email with baby's information and test results. Follow-up team will document information on white phone slip.
 - b) Follow-up team will print out baby's information from DHEL database on a yellow sheet of paper, attach the white phone slip and write the appropriate abnormal test and the result on yellow sheet.
 - c) If test results are emailed, follow-up team will print results and attach to yellow paper.
 - d) Follow-up team will enter infant's demographic data and reported test results into Access database under Fatty Acid Disorders.
 - e) Follow-up team will call healthcare provider listed on report and:
 - i) Verify that they are seeing the baby.
 - ii) Inform them of results.
 - iii) Ask them to get a repeat NBS card submitted to the KS lab.
 - iv) Confirm doctor's fax number.
 - v) Inform them that a letter will be faxed to their office with the results and instructions.
 - f) Follow-up team will print appropriate fatty acid low risk letter and fax (or mail, if no fax) to healthcare provider.
 - g) Follow-up team will print fatty acid parent letter and fatty acid parent information sheet and mail to baby's parents to inform them that their child has an abnormal result. NOTE: If infant is in the NICU, no parent letter is sent.
 - h) Follow-up team will enter data into Excel spreadsheet "Presumptive Totals" located on the "H" drive.
 - i) Lab will fax or mail results to doctor listed on NBS card. Lab will fax results to follow-up team. Report is attached to yellow sheet.
 - j) Follow-up team will enter lab information into WebIZ and set a follow-up reminder for 1 month from date of letter. NOTE: Name changes are documented on the copy of the lab report. Surname changes are also documented in WebIZ as an alias.
 - k) When complete, paperwork is filed by infant's date of birth.
- 4) If the results are considered **Moderate Risk (MR)** or **High Risk (HR)**:
 - a) Lab will contact follow-up team via phone and/or email with baby's information and test results. Follow-up team will document information on white phone slip.
 - b) Follow-up team will print out baby's information from DHEL database on a green sheet of paper, attach the white phone slip and write the appropriate abnormal test

- and the result on green sheet.
- c) If test results are emailed, follow-up team will print results and attach to green paper.
 - d) Follow-up team will enter infant's demographic data and reported test results into Access database under Fatty Acid Disorders.
 - e) Follow-up team will call healthcare provider listed on report and:
 - i) Verify that they are seeing the baby.
 - ii) Inform them of results.
 - iii) Ask them to notify parents and arrange appointment with specialist.
 - iv) Confirm doctor's fax number.
 - v) Inform them that a letter will be faxed to their office with the results and instructions.
 - f) Follow-up team will print appropriate fatty acid moderate or high risk letter and physician report form and fax (or mail, if no fax) to healthcare provider.
 - g) Follow-up team will print fatty acid parent letter and fatty acid parent information sheet and mail to baby's parents to inform them that their child has an abnormal result. NOTE: If infant is in the NICU, no parent letter is sent.
 - h) Follow-up team will enter data into Excel spreadsheet "Presumptive Totals" located on the "H" drive.
 - i) Lab will fax or mail results to doctor listed on NBS card.
 - j) Lab will fax results to follow-up team. Report is attached to green sheet.
 - k) Follow-up team will enter lab information into WebIZ and set a follow-up reminder for 1 month from date of letter. NOTE: Name changes are documented on the copy of the lab report. Surname changes are also documented in WebIZ as an alias.
 - l) When complete, paperwork is filed by infant's date of birth.



NEWBORN SCREENING ACT SHEET

SCREEN FOR: DECREASED C0 AND OTHER ALCYLCARNITINES

CONDITION: CARNITINE UPTAKE DEFECT (CUD)

DIFFERENTIAL DIAGNOSIS: Carnitine uptake defect (CUD).

METABOLIC DESCRIPTION: CUD is caused by a defect in the Carnitine transporter that moves Carnitine across the plasma membrane. Reduced Carnitine limits acylcarnitine formation preventing transport of fatty acids into the mitochondria, thereby limiting energy production. Tissues with high energy needs (skeletal and heart muscle) are particularly affected.

MEDICAL EMERGENCY - ACTION TO BE TAKEN IMMEDIATELY:

- Contact family to inform them of the newborn screening result and ascertain clinical status (poor feeding, lethargy, tachypnea.)
- Consult with pediatric metabolic specialist.
- Evaluate the newborn (tachycardia, hepatomegaly, reduced muscle tone); initiate emergency treatment as indicated by metabolic specialist.
- Initiate timely confirmatory/diagnostic testing as recommended by specialist.
- Educate family about signs, symptoms and need for urgent treatment if infant becomes ill.
- Report findings to newborn screening program.

CONFIRMATION OF DIAGNOSIS: Plasma and urine Carnitine analysis will reveal decreased free and total **carnitine (C0)** in plasma and over excretion of carnitine in urine. The newborns mother should be investigated as well because several cases of maternal CUD have been identified following an abnormal newborn screening result in their offspring. Transporter assays and OCTN2 gene sequencing establish the diagnosis.

CLINICAL EXPECTATIONS: Carnitine transporter defect has a variable expression and variable age of onset. Characteristic manifestations include lethargy, hypotonia, hepatomegaly, and cardiac decompensation due to cardiomyopathy. Hypoglycemia is typical in acute episodes.

REPORTING: Report diagnostic result to family and Kansas NBS program.

SPECIALIST:

Dr. Majed Dasouki
KU Medical Center
Kansas City, KS

Office: 913-588-6326
FAX: 913-588-6288

DISCLAIMER: These standards and guidelines were adapted from the American College of Medical Genetics ACT sheets. They are designed primarily as an educational resource for physicians to help them provide quality medical services. Adherence to these standards and guidelines does not necessarily ensure a successful medical outcome. These standards and guidelines should not be considered inclusive of all proper procedures and tests or exclusive of other procedures and tests that are reasonable directed to obtaining the same results. In determining the propriety of any specific procedure or test, the healthcare provider should apply his or her own professional judgment to the specific clinical circumstances presented by the individual patient or specimen. It may be prudent, however, to document in the patient's record the rationale for any significant deviation from these standards and guidelines



NEWBORN SCREENING ACT SHEET

SCREEN FOR: ELEVATED C16-OH +/- C18:1-OH AND OTHER LONG CHAIN ACYLCARNITINES

CONDITION: LONG-CHAIN 3-HYDROXYACYL-CoA DEHYDROGENASE DEFICIENCY (LCHADD) OR TRIFUNCTIONAL PROTEIN DEFICIENCY (TFP)

DIFFERENTIAL DIAGNOSIS: Long-chain 3-hydroxyacyl-CoA dehydrogenase deficiency (LCHADD); Trifunctional protein deficiency (TFP).

METABOLIC DESCRIPTION: LCHAD and TFP deficiencies are fatty acid oxidation (FAO) disorders. FAO occurs during prolonged fasting and/or periods of increased energy demands (fever, stress) after glycogen stores become depleted and energy production relies increasingly on fat metabolism. Fatty acids and potentially toxic derivatives accumulate in FAO disorders which are caused by deficiency in one of the enzymes involved in FAO.

ACTION TO BE TAKEN IMMEDIATELY:

- Contact family to inform them of the newborn screening result and ascertain clinical status (poor feeding, vomiting and lethargy).
- Consult with pediatric metabolic specialist.
- Evaluate infant (Hepatomegaly, cardiac insufficiency; history of sudden unexpected death in a sibling, maternal liver disease during pregnancy; hypoglycemia). If signs are present or infant is ill, initiate emergency treatment in consultation with metabolic specialist.
- Educate family about signs and symptoms of hypoglycemia and metabolic acidosis.
- Report findings to newborn screening program.

CONFIRMATION OF DIAGNOSIS: Hypoglycemia, elevated liver transaminases, bilirubin, lactate, ammonia, and creatine phosphokinase (CPK) are suggestive of LCHAD and TFP deficiencies. Plasma acylcarnitine and urine organic acid analysis are first-line tests to determine if the appropriate LCHAD/TFP profiles are present. Differentiation between both disorders requires further biochemical and molecular genetic testing in cultured fibroblasts derived from a skin biopsy.

CLINICAL EXPECTATIONS: LCHAD and TFP deficiencies typically present acutely and are associated with high mortality unless treated promptly; milder variants exist. Hallmark features include hepatomegaly, cardiomyopathy, lethargy, hypoketotic hypoglycemia, elevated liver transaminases, lactic acidosis, and failure to thrive.

REPORTING: Report diagnostic result to family and Kansas NBS program.

SPECIALIST:

Dr. Majed Dasouki
KU Medical Center
Kansas City, KS

Office: 913-588-6326
FAX: 913-588-6288

DISCLAIMER: These standards and guidelines were adapted from the American College of Medical Genetics ACT sheets. They are designed primarily as an educational resource for physicians to help them provide quality medical services. Adherence to these standards and guidelines does not necessarily ensure a successful medical outcome. These standards and guidelines should not be considered inclusive of all proper procedures and tests or exclusive of other procedures and tests that are reasonable directed to obtaining the same results. In determining the propriety of any specific procedure or test, the healthcare provider should apply his or her own professional judgment to the specific clinical circumstances presented by the individual patient or specimen. It may be prudent, however, to document in the patient's record the rationale for any significant deviation from these standards and guidelines

Kansas Newborn Screening Program



NEWBORN SCREENING ACT SHEET

SCREEN FOR: ELEVATED C8 WITH LESSER ELEVATIONS OF C6 AND C10 ACYLCARNITINE

CONDITION: MEDIUM-CHAIN ACYL-COA DEHYDROGENASE DEFICIENCY (MCADD)

DIFFERENTIAL DIAGNOSIS: Medium-chain acyl-CoA dehydrogenase deficiency (MCADD).

METABOLIC DESCRIPTION: MCAD deficiency is a fatty acid oxidation (FAO) disorder. FAO occurs during prolonged fasting and/or periods of increased energy demands (fever, stress) when energy production relies increasingly on fat metabolism. In an FAO disorder, fatty acids and potentially toxic derivatives accumulate because of a deficiency in one of the mitochondrial FAO enzymes.

MEDICAL EMERGENCY - ACTION TO BE TAKEN IMMEDIATELY:

- Contact family to inform them of the newborn screening result and ascertain clinical status (poor feeding, vomiting, and lethargy).
- Consult with pediatric metabolic specialist.
- Evaluate the newborn (poor feeding, lethargy, hypotonia, and hepatomegaly). If signs are present or infant is ill, initiate emergency treatment with IV glucose. Transport to hospital for further treatment in consultation with metabolic specialist. If infant is normal initiate timely confirmatory/diagnostic testing, as recommended by specialist.
- Educate family about need for infant to avoid fasting. Even if mildly ill, immediate treatment with IV glucose is needed.
- Report findings to newborn screening program.

CONFIRMATION OF DIAGNOSIS: Plasma acylcarnitine analysis will show elevated octanoylcarnitine (C8). Urine acylglycine will show elevated hexanoylglycine. Diagnosis is confirmed by mutation analysis of the MCAD gene.

CLINICAL EXPECTATIONS: MCAD deficiency is usually asymptomatic in the newborn although it can present acutely in the neonate with hypoglycemia, metabolic acidosis, hyperammonemia, and hepatomegaly. MCAD deficiency is associated with high mortality unless treated promptly; milder variants exist. Hallmark features include vomiting, lethargy, and hypoketotic hypoglycemia. It is a significant cause of sudden death.

REPORTING: Report diagnostic result to family and Kansas NBS program.

SPECIALIST:

Dr. Majed Dasouki
KU Medical Center
Kansas City, KS

Office: 913-588-6326
FAX: 913-588-6288

DISCLAIMER: These standards and guidelines were adapted from the American College of Medical Genetics ACT sheets. They are designed primarily as an educational resource for physicians to help them provide quality medical services. Adherence to these standards and guidelines does not necessarily ensure a successful medical outcome. These standards and guidelines should not be considered inclusive of all proper procedures and tests or exclusive of other procedures and tests that are reasonable directed to obtaining the same results. In determining the propriety of any specific procedure or test, the healthcare provider should apply his or her own professional judgment to the specific clinical circumstances presented by the individual patient or specimen. It may be prudent, however, to document in the patient's record the rationale for any significant deviation from these standards and guidelines



NEWBORN SCREENING ACT SHEET

SCREEN FOR: ELEVATED C14:1 +/- OTHER LONG-CHAIN
ACYLCARNITINES

CONDITION: VERY LONG CHAIN ACYL-COA DEHYDROGENASE
DEFICIENCY (VLCADD)

DIFFERENTIAL DIAGNOSIS: Very long-chain acyl-CoA dehydrogenase deficiency (VLCADD).

METABOLIC DESCRIPTION: VLCAD deficiency is a fatty acid oxidation (FAO) disorder. Fatty acid oxidation occurs during prolonged fasting and/or periods of increased energy demands (fever, stress) when energy production relies increasingly on fat metabolism. In a FAO disorder, fatty acids and potentially toxic derivatives accumulate because of a deficiency in one of the mitochondrial FAO enzymes.

MEDICAL EMERGENCY - ACTION TO BE TAKEN IMMEDIATELY:

- Contact family to inform them of the newborn screening result and ascertain clinical status (poor feeding, vomiting, and lethargy).
- Consult with pediatric metabolic specialist.
- Evaluate the newborn (poor feeding, lethargy, hypotonia, hepatomegaly, arrhythmia, evidence of cardiac decompensation). If signs are present or infant is ill, initiate emergency treatment with IV glucose and oxygen. Transport to hospital for further treatment in consultation with metabolic specialist. If infant is normal initiate timely confirmatory/ diagnostic testing, as recommended by specialist.
- Educate family about need for infant to avoid fasting. Even if mildly ill, immediate treatment with IV glucose is needed.
- Report findings to newborn screening program.

CONFIRMATION OF DIAGNOSIS: Plasma acylcarnitine profile may show increased C14:1 acylcarnitine (and lesser elevations of other long chain acylcarnitines). Diagnosis is confirmed in consultation with the metabolic specialist by mutation analysis of the VLCAD gene and additional biochemical genetic tests.

CLINICAL EXPECTATIONS: VLCAD deficiency may present acutely in the neonate and is associated with high mortality unless treated promptly; milder variants exist. Features of severe VLCAD deficiency in infancy include hepatomegaly, cardiomyopathy and arrhythmias, lethargy, hypoketotic hypoglycemia and failure to thrive. Treatment is available.

REPORTING: Report diagnostic result to family and Kansas NBS program.

SPECIALIST:

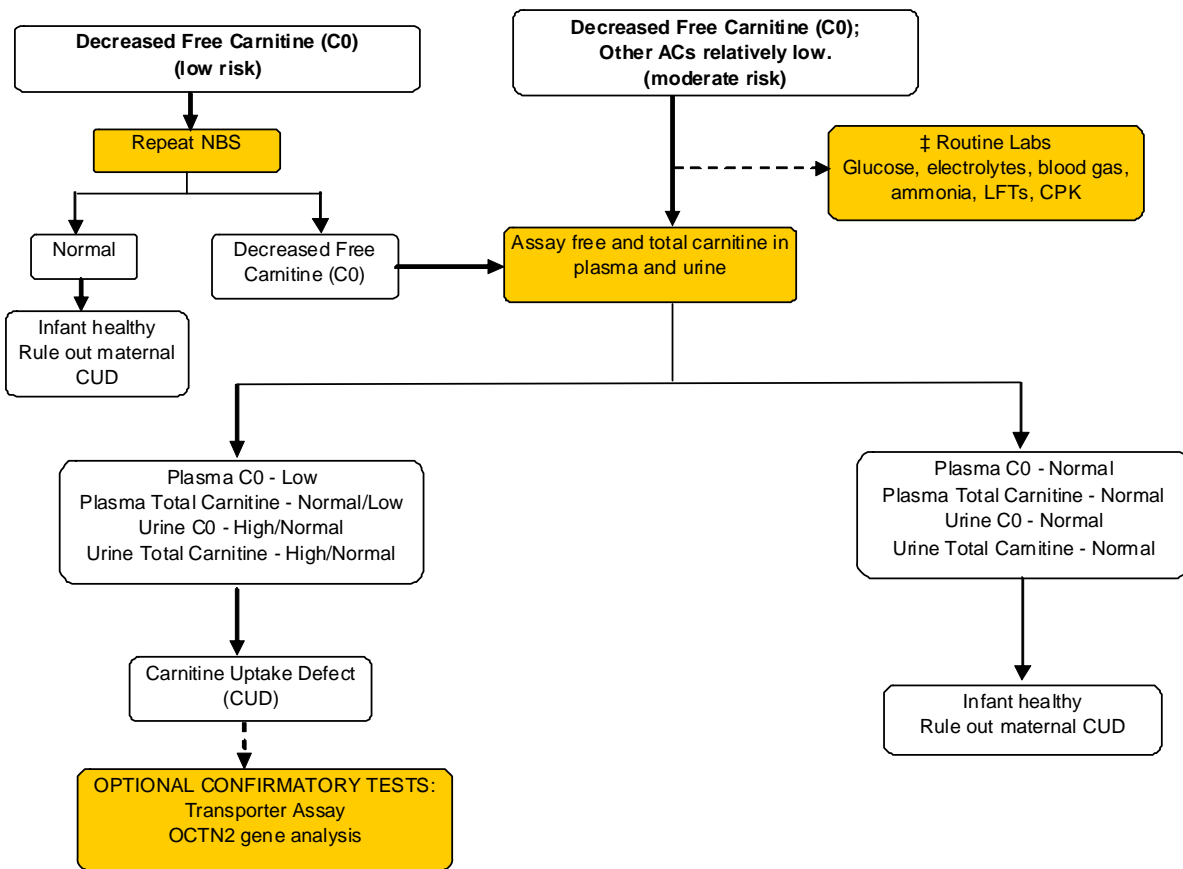
Dr. Majed Dasouki
KU Medical Center
Kansas City, KS

Office: 913-588-6326
FAX: 913-588-6288

DISCLAIMER: These standards and guidelines were adapted from the American College of Medical Genetics ACT sheets. They are designed primarily as an educational resource for physicians to help them provide quality medical services. Adherence to these standards and guidelines does not necessarily ensure a successful medical outcome. These standards and guidelines should not be considered inclusive of all proper procedures and tests or exclusive of other procedures and tests that are reasonable directed to obtaining the same results. In determining the propriety of any specific procedure or test, the healthcare provider should apply his or her own professional judgment to the specific clinical circumstances presented by the individual patient or specimen. It may be prudent, however, to document in the patient's record the rationale for any significant deviation from these standards and guidelines



C0 (FREE CARNITINE) LOW



Abbreviations/Key

AC = acylcarnitine

CPK = creatine phosphokinase

CUD = carnitine uptake defect

LFTs = liver function tests

NBS = Newborn Screening

OCTN2 = organic cation transporter 2

Action steps are shown in gold (shaded) boxes; results are in plain boxes.

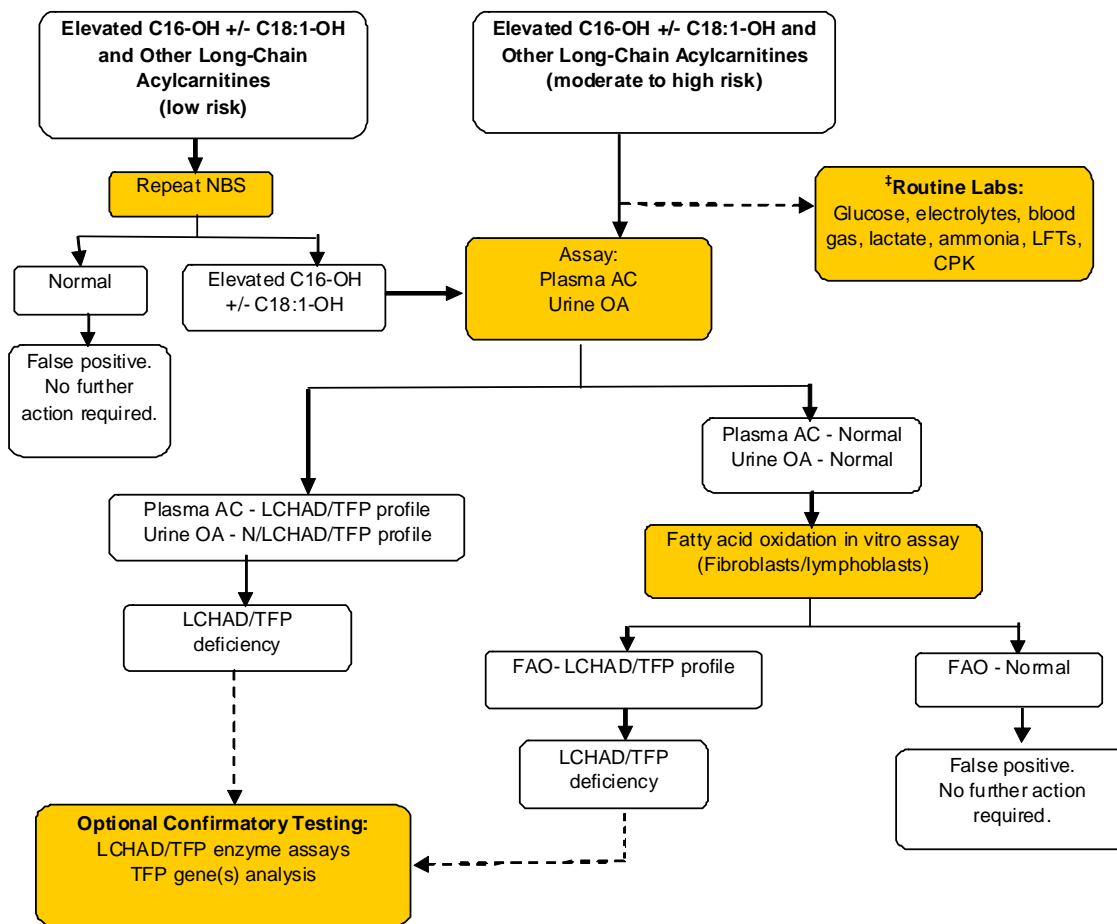
Dash lines indicate optional steps

‡ = When the positive predictive value of screening is sufficiently high and the risk to the infant is high, some initiate diagnostic studies that are locally available at the same time as confirmation of the screening result is done.

DISCLAIMER: These algorithms and guidelines were adapted from the American College of Medical Genetics algorithm sheets. They are designed primarily as an educational resource for physicians to help them provide quality medical services. Adherence to these standards and guidelines does not necessarily ensure a successful medical outcome. These standards and guidelines should not be considered inclusive of all proper procedures and tests or exclusive of other procedures and tests that are reasonable directed to obtaining the same results. In determining the propriety of any specific procedure or test, the healthcare provider should apply his or her own professional judgment to the specific clinical circumstances presented by the individual patient or specimen. It may be prudent, however, to document in the patient's record the rationale for any significant deviation from these standards and guidelines



ELEVATED C16-OH +/- C18:1-OH AND OTHER LONG-CHAIN ACYLCARNITINES



Action steps are shown in gold (shaded) boxes; results are in plain boxes. Dash lines indicate optional steps

Abbreviations/Key

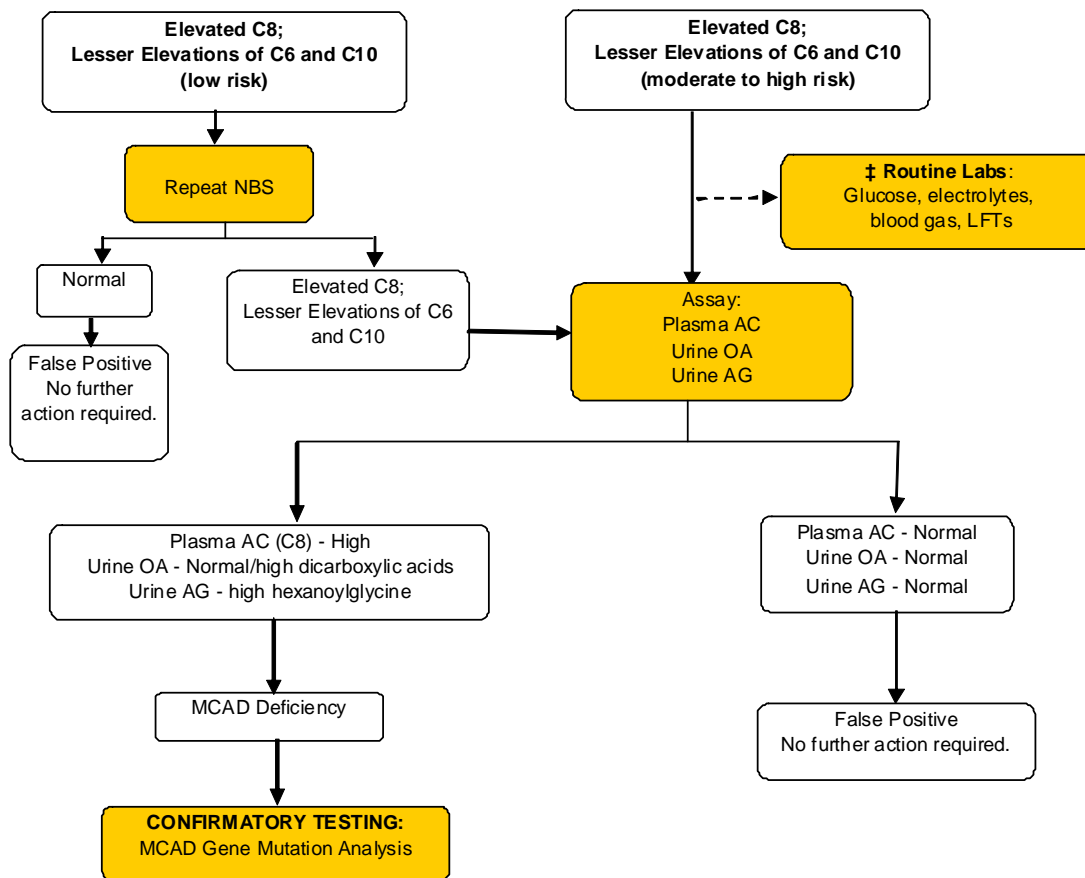
- AC = acylcarnitine
- CPK - creatine phosphokinase
- FAO = fatty acid oxidation
- LCHAD = Long-chain 3-hydroxyacyl-CoA dehydrogenase
- LFTs = liver function tests
- NBS = Newborn Screening
- OA = organic acids
- TFP = Trifunctional protein

‡ = When the positive predictive value of screening is sufficiently high and the risk to the baby is high, some initiate diagnostic studies that are locally available at the same time as confirmation of the screening result is done.

DISCLAIMER: These algorithms and guidelines were adapted from the American College of Medical Genetics algorithm sheets. They are designed primarily as an educational resource for physicians to help them provide quality medical services. Adherence to these standards and guidelines does not necessarily ensure a successful medical outcome. These standards and guidelines should not be considered inclusive of all proper procedures and tests or exclusive of other procedures and tests that are reasonable directed to obtaining the same results. In determining the propriety of any specific procedure or test, the healthcare provider should apply his or her own professional judgment to the specific clinical circumstances presented by the individual patient or specimen. It may be prudent, however, to document in the patient's record the rationale for any significant deviation from these standards and guidelines



ELEVATED C8 + LESSER ELEVATIONS OF C6 & C10



Abbreviations/Key

AC = acylcarnitine

AG = acylglycine

LFTs = liver function tests

MCAD = Medium-chain acyl-CoA dehydrogenase

NBS = Newborn Screening

OA = organic acid

‡ = When the positive predictive value of screening is sufficiently high and the risk to the newborn is high, some initiate diagnostic studies that are locally available at the same time as confirmation of the screening result is done.

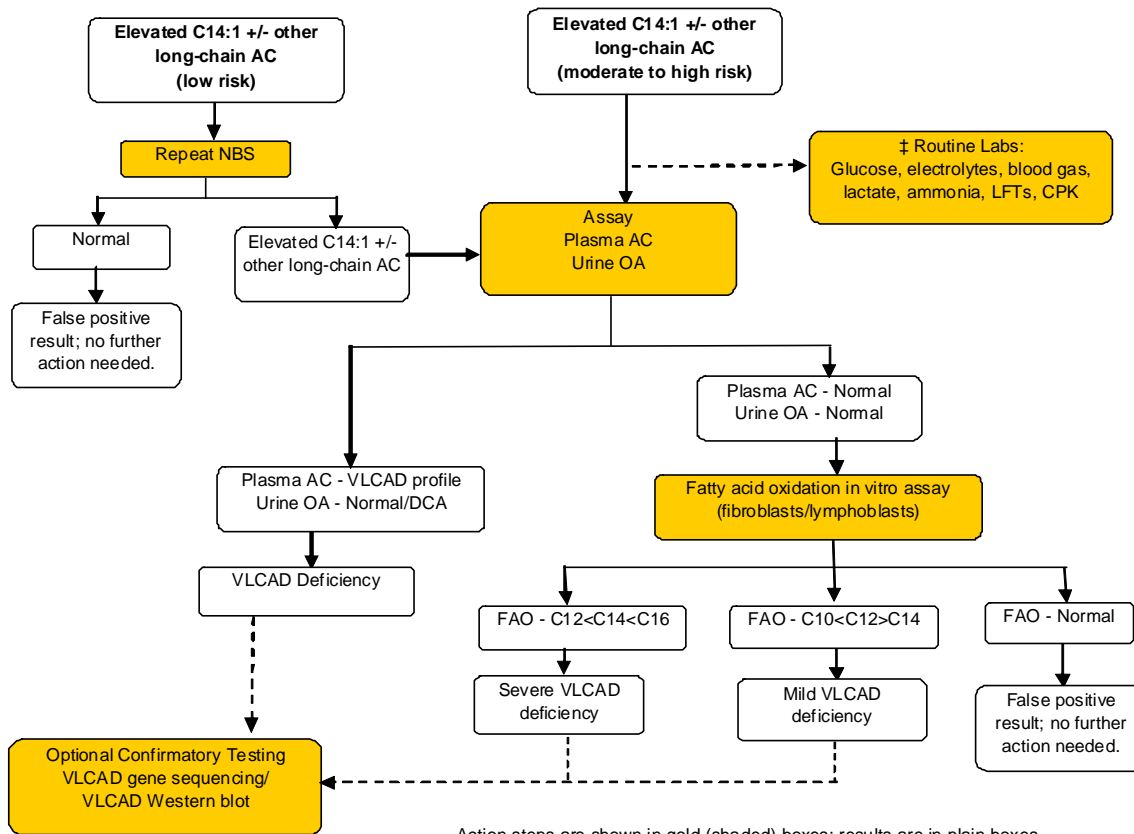
Action steps are shown in gold (shaded) boxes; results are in plain boxes.

Dash lines indicate optional steps.

DISCLAIMER: These algorithms and guidelines were adapted from the American College of Medical Genetics algorithm sheets. They are designed primarily as an educational resource for physicians to help them provide quality medical services. Adherence to these standards and guidelines does not necessarily ensure a successful medical outcome. These standards and guidelines should not be considered inclusive of all proper procedures and tests or exclusive of other procedures and tests that are reasonable directed to obtaining the same results. In determining the propriety of any specific procedure or test, the healthcare provider should apply his or her own professional judgment to the specific clinical circumstances presented by the individual patient or specimen. It may be prudent, however, to document in the patient's record the rationale for any significant deviation from these standards and guidelines



ELEVATED C14:1 +/- OTHER LONG CHAIN AC



Action steps are shown in gold (shaded) boxes; results are in plain boxes. Dash lines indicate optional steps

Abbreviations

AC = acylcarnitine
 CPK = creatine phosphokinase
 DCA = dicarboxylic acid
 FAO = fatty acid oxidation
 LFTs = liver function tests
 NBS = Newborn Screening
 OA = organic acid
 VLCAD = very long-chain acyl-CoA dehydrogenase

Key

‡ When positive predictive value of screening is sufficiently high and the risk to the baby is high, some initiate diagnostic studies that are locally available at the same time as the confirmation of the screening result is done.

DISCLAIMER: These algorithms and guidelines were adapted from the American College of Medical Genetics algorithm sheets. They are designed primarily as an educational resource for physicians to help them provide quality medical services. Adherence to these standards and guidelines does not necessarily ensure a successful medical outcome. These standards and guidelines should not be considered inclusive of all proper procedures and tests or exclusive of other procedures and tests that are reasonable directed to obtaining the same results. In determining the propriety of any specific procedure or test, the healthcare provider should apply his or her own professional judgment to the specific clinical circumstances presented by the individual patient or specimen. It may be prudent, however, to document in the patient's record the rationale for any significant deviation from these standards and guidelines

EXAMPLE OF 1ST LETTER SENT TO PHYSICIAN FOR LOW RISK FATTY ACID DISORDERS



Mark Parkinson, Governor
Roderick L. Bremby, Secretary

DEPARTMENT OF HEALTH
AND ENVIRONMENT

www.kdheks.gov

**Abnormal C8 Lab Report
Kansas Newborn Screening Program**

Date

Doctor's Name
Address Line 1
Address Line 2

RE: Baby's Name
DOB: xx/xx/xxxx

MOTHER'S NAME: Mother's Name
PHONE NUMBER: xxx-xxx-xxxx

Specimen date: xx/xx/xxxx

C8: Result $\mu\text{mol/L}$
Expected ranges: $< 0.38 \mu\text{mol/L}$

The newborn screening result above is consistent with a **low** risk for Medium-Chain Acyl-CoA Dehydrogenase deficiency (MCADD). The level for C8 is considered to be indeterminate because MCADD cannot be ruled out. Increased analyte levels may be seen if the specimen is collected from an infant less than 24 hours of age; a premature infant; or an acutely ill infant.

The final newborn screening lab report will be sent when all testing is completed.

RECOMMENDATION:

Repeat the screening test within 1 to 3 days of receiving this notice, and send the specimen to the State lab for analysis. (If the baby was transfused, repeat the screening on day 4 after transfusion). If the repeat screen is positive or indeterminate, additional testing and consultation with a specialist will be required.

In accordance with Kansas Administrative Regulation 28-4-502, it is the responsibility of the attending physician or other birth attendant to obtain repeat specimens when needed to complete the screening process.

For consultation, please contact:

Dr. Majed Dasouki
KU Medical Center
Kansas City
Office 913-588-6326

Additional information is available on the Kansas Newborn Screening Website at:
http://www.kdheks.gov/newborn_screening/info_professionals.htm.

You may contact the Newborn Screening Program at (785) 291-3363 or 1-800-332-6262 if you have any questions or concerns.

EXAMPLE OF 1ST LETTER SENT TO PHYSICIAN FOR MODERATE RISK FATTY ACID DISORDERS



Mark Parkinson, Governor
Roderick L. Bremby, Secretary

DEPARTMENT OF HEALTH
AND ENVIRONMENT

www.kdheks.gov

**Abnormal C8, C6, C10:1 Lab Report
Kansas Newborn Screening Program**

Date

Doctor's Name
Address Line 1
Address Line 2

RE: Baby's Name
DOB: xx/xx/xxxx
Specimen date: xx/xx/xxxx

MOTHER'S NAME: Mother's Name
PHONE NUMBER: xxx-xxx-xxxx

Results **C8:** Result $\mu\text{mol/L}$ **C6:** Result $\mu\text{mol/L}$ **C10:1:** Result $\mu\text{mol/L}$
Expected ranges: C8: < 0.38 $\mu\text{mol/L}$ C6: < 0.16 $\mu\text{mol/L}$ C10:1: < 0.36 $\mu\text{mol/L}$

The newborn screening results above are consistent with a **moderate** risk for Medium-Chain Acyl-CoA Dehydrogenase deficiency (MCADD). The levels for C8, C6 and C10:1 are considered to be indeterminate because MCADD cannot be ruled out. Increased analyte levels may be seen if the specimen is collected from an infant less than 24 hours of age; a premature infant; or an acutely ill infant.

The final newborn screening lab report will be sent when all testing is completed.

RECOMMENDATION:

Immediate consultation with the consultant listed below is essential for diagnostic testing and genetic counseling. Please call to arrange an immediate appointment.

In accordance with Kansas Administrative Regulation 28-4-502, it is the responsibility of the attending physician or other birth attendant to obtain repeat specimens when needed to complete the screening process.

For consultation, please contact:

Dr. Majed Dasouki
KU Medical Center
Kansas City
Office 913-588-6326

Additional information is available on the Kansas Newborn Screening Website at:
http://www.kdheks.gov/newborn_screening/info_professionals.htm.

You may contact the Newborn Screening Program at (785) 291-3363 or 1-800-332-6262 if you have any questions or concerns.

EXAMPLE OF 1ST LETTER SENT TO PHYSICIAN FOR HIGH RISK FATTY ACID DISORDERS



Mark Parkinson, Governor
Roderick L. Bremby, Secretary

DEPARTMENT OF HEALTH
AND ENVIRONMENT

www.kdheks.gov

**Abnormal C8, C6, C10:1 Lab Report
Kansas Newborn Screening Program**

Date

Doctor's Name
Address Line 1
Address Line 2

RE: Baby's Name
DOB: xx/xx/xxxx

MOTHER'S NAME: Mother's Name
PHONE NUMBER: xxx-xxx-xxxx

Specimen date: 12/31/2008

Results:	C8: Result $\mu\text{mol/L}$	C6: Result $\mu\text{mol/L}$	C10:1: Result $\mu\text{mol/L}$
Expected range:	C8: < 0.38 $\mu\text{mol/L}$	C6: < 0.16 $\mu\text{mol/L}$	C10:1: < 0.36 $\mu\text{mol/L}$

The newborn screening results above are **highly suggestive** of Medium-Chain Acyl-CoA Dehydrogenase deficiency (MCADD). Untreated infants with MCADD may appear healthy, but can present acutely with hypoglycemia, metabolic acidosis, hyperammonemia, and hepatomegaly. MCAD deficiency is associated with high mortality unless treated promptly. Hallmark features include vomiting, lethargy, and hypoketotic hypoglycemia.

The final newborn screening lab report will be sent when all testing is completed.

RECOMMENDATION:

Immediate consultation with the consultant listed below is essential for diagnostic testing and genetic counseling. Please call to arrange an immediate appointment.

In accordance with Kansas Administrative Regulation 28-4-502, it is the responsibility of the attending physician or other birth attendant to obtain repeat specimens when needed to complete the screening process.

For consultation, please contact:

Dr. Majed Dasouki
KU Medical Center
Kansas City
Office 913-588-6326
Pager 913-917-3647

PLEASE COMPLETE AND RETURN THE ENCLOSED PHYSICIAN REPORTING FORM WHEN FOLLOW UP IS COMPLETE.

Additional information is available on the Kansas Newborn Screening Website at:
http://www.kdheks.gov/newborn_screening/info_professionals.htm.

You may contact the Newborn Screening Program at (785) 291-3363 or 1-800-332-6262 if you have any questions or concerns.

EXAMPLE OF LETTER TO PHYSICIANS FOR MULTIPLE LOW OR MODERATE RISK MS/MS RESULTS



Mark Parkinson, Governor
Roderick L. Bremby, Secretary

DEPARTMENT OF HEALTH
AND ENVIRONMENT

www.kdheks.gov

**Multiple Elevated MS/MS Analytes Lab Report
Kansas Newborn Screening Program**

Date

Doctor's Name
Address Line 1
Address Line 2

RE: Baby's Name
DOB: xx/xx/xxxx

MOTHER'S NAME: Mother's Name
PHONE NUMBER: xxx-xxx-xxxx

Specimen date: xx/xx/xxxx

The above infant has multiple MS/MS analyte results that are within the low-moderate risk range. The elevated results may be due to TPN or other supplements, but further testing is required to identify any true positive results.

Analyte	Result (µmol/L)	Expected Range (µmol/L)	Associated Disorder
Phenylalanine	Result	< 128	PKU
Leucine	Result	< 250	MSUD
Methionine	Result	< 79	HCY
Tyrosine	Result	< 260	TYR I
Argininosuccinic Acid	Result	< 0.60	ASA
Citrulline	Result	< 53	CIT
C8	Result	< 0.38	MCADD
C14:1	Result	< 0.66	VLCADD
C16-OH	Result	< 0.12	LCHAD/TFP
C0	Result	> 14.5	CUD
C5	Result	< 0.71	IVA
C5DC	Result	< 0.32	GA-1
C5-OH	Result	< 0.61	3MCC, HMG, BKT AND MCD
C3	Result	< 6.6	PROP, MUT, Cbl A&B

NR = No Result reported at this time

RECOMMENDATION:

Infant should be off TPN or other dietary supplements for 48 hours prior to retest. Repeat the screening test and send the specimen to the State lab for analysis. (If the baby was transfused, repeat the screening on day 4 after transfusion). If the repeat screen is positive or indeterminate, additional testing and consultation with a specialist will be required.

In accordance with Kansas Administrative Regulation 28-4-502, it is the responsibility of the attending physician or other birth attendant to obtain repeat specimens when needed to complete the screening process.

Additional information is available on the Kansas Newborn Screening Website at:
http://www.kdheks.gov/newborn_screening/info_professionals.htm.

You may contact the Newborn Screening Program at (785) 291-3363 or 1-800-332-6262 if you have any questions or concerns.

EXAMPLE OF CUD PHYSICIAN'S REPORTING FORM



Mark Parkinson, Governor
Roderick L. Bremby, Secretary

DEPARTMENT OF HEALTH
AND ENVIRONMENT

www.kdheks.gov

**DECREASED CO +/- other Acylcarnitines (Possible CUD)
NEWBORN SCREENING
PHYSICIAN REPORTING FORM**

****Return this form When Follow-Up is Complete ****

Date

Doctor's Name
Address Line 1
Address Line 2

If this infant is not a current patient of this practice, record name and contact information for Primary Care Physician and return this form.

RE: Baby's Name
DOB: xx/xx/xxxx

Baby's name if different than listed

DIAGNOSIS EXCLUDED: Date Excluded: _____

Baby does **NOT** have Carnitine Uptake Defect

DIAGNOSIS CONFIRMED: Date Diagnosis Confirmed: _____

Baby has Carnitine Uptake Defect

Lab Results: (please fill in and attach a copy of specialist's report)

Plasma free and total carnitine: _____

Urine free and total carnitine: _____

Additional lab results: _____

Date treatment began: _____

Baby referred to specialist (please attach copy of specialist's report)

Name of specialist: _____

FORM CONTINUES ON BACK

Kansas Newborn Screening Program

EXAMPLE OF LCHADD/TFP PHYSICIAN'S REPORTING FORM



Mark Parkinson, Governor
Roderick L. Bremby, Secretary

DEPARTMENT OF HEALTH
AND ENVIRONMENT

www.kdheks.gov

**ELEVATED C16-OH +/- C18:1-OH (Possible LCHADD / TFP)
NEWBORN SCREENING
PHYSICIAN REPORTING FORM**

****Return this form When Follow-Up is Complete ****

Date

Doctor's Name
Address Line 1
Address Line 2

If this patient is not a current patient of this practice, record name and contact information for Primary Care Physician and return this form.

RE: Baby's Name
DOB: xx/xx/xxxx

Baby's name if different than listed

DIAGNOSIS EXCLUDED: Date Excluded: _____

Baby does **NOT** have LCHADD or TFP

DIAGNOSIS CONFIRMED: Date Diagnosis Confirmed: _____

Baby has LCHADD or TFP (circle one)

Lab Results: (please fill in and attach a copy of specialist's report)

Acylcarnitine profile: _____

Urine organic acids: _____

Additional lab results: _____

Date treatment began: _____

Baby referred to specialist (please attach copy of specialist's report)

Name of specialist: _____

FORM CONTINUES ON BACK

Kansas Newborn Screening Program

UNABLE TO COMPLETE SCREENING PROCESS:

- Parent notified of abnormal lab by registered letter and did not follow-up
 - o Date letter sent: _____
- Parent notified of abnormal lab at office visit and did not follow-up
 - o Date of office visit: _____

ADDITIONAL COMMENTS:

Physician Signature _____ **Date** _____

When LCHADD or TFP is confirmed, the Kansas Law 65-180 through 65-183 requires reporting by physician. Financial assistance for metabolic clinic services and treatments may be available to the family upon application to the Children & Youth with Special Health Care Needs (CYSHCN) program. A CYSHCN application will be sent to the baby's address. Parents or physicians can call CYSHCN at 1-800-332-6262 or 1-785-296-1313 for more information

Baby's most recent address:

Parent or Guardian _____

Address _____
Street/PO Box City State Zip

EXAMPLE OF MCADD PHYSICIAN'S REPORTING FORM



Mark Parkinson, Governor
Roderick L. Bremby, Secretary

DEPARTMENT OF HEALTH
AND ENVIRONMENT

www.kdheks.gov

**ELEVATED C8; LESSER ELEVATION C6, C10 (Possible MCADD)
NEWBORN SCREENING
PHYSICIAN REPORTING FORM**

****Return this form When Follow-Up is Complete ****

Date

Doctor's Name
Address Line 1
Address Line 2

If this infant is not a current patient of this practice, record name and contact information for Primary Care Physician and return this form.

RE: Baby's Name
DOB: xx/xx/xxxx

Baby's name if different than listed

DIAGNOSIS EXCLUDED: Date Excluded: _____

Baby does **NOT** have MCADD

DIAGNOSIS CONFIRMED: Date Diagnosis Confirmed: _____

Baby has MCADD

Lab Results: (please fill in and attach a copy of specialist's report)

Acylcarnitine profile: _____

Urine organic acids: _____

Additional lab results: _____

Date treatment began: _____

Baby referred to specialist (please attach copy of specialist's report)

Name of specialist: _____

FORM CONTINUES ON BACK

EXAMPLE OF VLCADD PHYSICIAN'S REPORTING FORM



Mark Parkinson, Governor
Roderick L. Bremby, Secretary

DEPARTMENT OF HEALTH
AND ENVIRONMENT

www.kdheks.gov

**ELEVATED C14:1 (Possible VLCADD)
NEWBORN SCREENING
PHYSICIAN REPORTING FORM**

****Return this form When Follow-Up is Complete ****

Date

Doctor's Name
Address Line 1
Address Line 2

If this infant is not a current patient of this practice, record name and contact information for Primary Care Physician and return this form.

RE: Baby's Name
DOB: xx/xx/xxxx

Baby's name if different than listed

DIAGNOSIS EXCLUDED: Date Excluded: _____

Baby does **NOT** have VLCADD

DIAGNOSIS CONFIRMED: Date Diagnosis Confirmed: _____

Baby has VLCADD

Lab Results: (please fill in and attach a copy of specialist's report)

Acylcarnitine profile: _____

Urine organic acids: _____

Additional lab results: _____

Date treatment began: _____

Baby referred to specialist (please attach copy of specialist's report)

Name of specialist: _____

FORM CONTINUES ON BACK

Kansas Newborn Screening Program



Carnitine Uptake Defect Information for Health Professionals

Carnitine uptake defect is a type of fatty acid oxidation disorder in which the enzyme carnitine transporter is missing or is not functioning correctly. Carnitine cannot be transported into cells leading to difficulty utilizing fats for energy.

✓ Clinical Symptoms

There are two forms of carnitine uptake defect; one beginning in infancy and one in childhood.

Symptoms of the infancy form begin between birth and age three. Metabolic crises can occur, particularly after fasting or periods of sickness/infection. Symptoms of a metabolic crisis include lethargy, behavior changes, feeding problems, diarrhea, fever, and hypoglycemia. If untreated, metabolic crisis can lead to breathing problems, brain swelling, seizures, coma, and death. If untreated, babies can also have cardiomegaly, skeletal muscle weakness, and anemia. Brain damage can result from repeated episodes of metabolic crisis.

Symptoms of the childhood form of carnitine uptake defect usually begin between the ages of 1 and 7. These children do not have metabolic crises. Symptoms of the childhood form include cardiomegaly, muscle weakness, and possibly heart failure and death if untreated.

✓ Incidence

Carnitine uptake defect occurs in less than 1 out of every 100,000 births.

✓ Genetics of carnitine uptake defect

Mutations in the OCTN2 gene cause carnitine uptake defect. Mutations in this gene cause a defect in carnitine transport across the plasma membrane and into cells. This limits acylcarnitine formation and limits energy production by preventing transport of fatty acids into the mitochondria.

✓ How do people inherit carnitine uptake defect?

Carnitine uptake defect is inherited in an autosomal recessive manner. Parents of an individual with an autosomal recessive condition each carry one copy of the mutated gene, but do not show signs and symptoms of the condition. Each pregnancy between carrier parents has a 25% chance of producing a child affected with carnitine uptake defect, a 50% chance of producing an unaffected carrier child, and a 25% chance of producing a child who is unaffected and is not a carrier.

✓ Treatment

Immediate diagnosis and treatment of carnitine uptake defect is critical to normal development and health. Treatment is usually effective if started early and continued throughout life. Recommended treatment is L-carnitine supplementation and avoidance of fasting. This treatment can reverse cardiomegaly. Individuals may benefit from a low-fat, high-carbohydrate diet.

✓ **Screening Methodology**

Primary screening for carnitine uptake defect utilizes tandem mass spectrometry. Individuals who screen positive for carnitine uptake defect will have low levels of carnitine, and very low levels of C0 (free carnitine).

✓ **What to do After Receiving Presumptive Positive CUD Screening Results**

MEDICAL EMERGENCY: TAKE THE FOLLOWING IMMEDIATE ACTIONS

- 1) **The clinician should immediately check on the clinical status of the baby.**
- 2) **Consultation with a metabolic specialist is essential.**
- 3) **The specialist may request confirmatory lab tests on the baby.**
- 4) **Call KS Newborn Screening Program at 785-291-3363 with questions about results.**
- 5) **Report Clinical Findings to Newborn Screening Program at 785-291-3363.**
- 6) **Same birth siblings (twins, triplets) of infants diagnosed with CUD should be re-screened; additional testing of these siblings also may be indicated.**
- 7) **Testing should be done for mothers of newborns with CUD because there have been cases of undiagnosed maternal CUD.**

✓ **Confirmation of Diagnosis**

The diagnosis of carnitine uptake defect is confirmed through plasma and urine carnitine analysis revealing a decreased level of free and total carnitine in plasma and an excess amount of carnitine in urine. Transporter analysis and gene sequencing may also be used to confirm the diagnosis.

✓ **Communication of Results to Parents**

If a baby has a presumptive positive carnitine uptake defect newborn screening result, additional testing needs to be performed to confirm a diagnosis. In accordance with Kansas Administrative Regulation 28-4-502, it is the responsibility of the attending physician or other birth attendant to obtain repeat specimens when needed to complete the screening process.

If a baby is diagnosed with CUD, the following points should be conveyed to parents:

- ***Parents should understand that treatment for carnitine uptake defect will be lifelong.***
- ***Parents should understand that treatment cannot necessarily prevent all health complications. Long-term management, monitoring, and compliance with treatment recommendations are essential to the child's well-being. A multidisciplinary approach is recommended and should include the following specialties: pediatrics and metabolic disease specialists.***
- ***Genetic counseling services may be indicated. A list of counselors and geneticists, whose services are available in Kansas, should be given to the parents if they have not already seen a geneticist.***

For consultation contact:

Dr. Majed Dasouki
KU Medical Center
Kansas City, KS
913-588-6326

11/24/08



Long Chain 3-hydroxyacyl-CoA Dehydrogenase (LCHAD) Deficiency Information for Healthcare Professionals

Long chain 3-hydroxyacyl-CoA dehydrogenase (LCHAD) deficiency is caused by an enzyme defect in the mitochondrial beta-oxidation cycle. This results in an inability of the body to break down long fatty acids into a usable energy source (ketones). Unrecognized, LCHAD deficiency may be rapidly progressive and fatal secondary to its cardiac involvement. It is classified as a fatty acid oxidation disorder.

✓ Clinical Symptoms

LCHAD can cause mild effects in some people and more serious health issues in others. Babies and children usually begin to have symptoms sometime from birth through age two. LCHAD deficiency causes episodes of hypoglycemia. This can include fatigue, hypotonia, nausea, vomiting, irritability, and behavior changes. If hypoglycemia is not treated, a child with LCHAD deficiency can develop respiratory problems, swelling of the brain, seizures and coma.

Symptoms often happen after fasting for more than a few hours. Symptoms are also more likely to occur when children get sick or have an infection. Between episodes of hypoglycemia, people with LCHAD deficiency are usually healthy; however, repeated episodes can cause brain damage. This can result in learning disabilities or mental retardation.

Babies and children who are not treated may have poor weight gain, delays in learning, delays in walking and other motor skills, enlarged liver and other liver problems, enlarged heart and other heart problems, and vision loss due to build-up of pigment in the retina.

Some children with LCHAD have never had symptoms and are only found to be affected after a brother or sister is diagnosed.

Mothers of babies with LCHAD deficiency may have problems during pregnancy. These problems may include anorexia, vomiting, abdominal pain, and jaundice during the third trimester of pregnancy. If untreated, it can cause HELLP syndrome or acute fatty liver of pregnancy (AFLP) and possibly the need for a liver transplant or even death. Less frequently, pregnancies with babies affected with other fatty acid oxidation disorders may be complicated by HELLP syndrome or AFLP.

✓ Incidence

LCHAD deficiency occurs in greater than 1 in 75,000 births. Incidence is likely higher in Finland where the carrier rate is 1:175.

✓ Genetics of LCHAD Deficiency

Mutations in the HADHA gene cause long-chain 3-hydroxyacyl-coenzyme A dehydrogenase deficiency. Mutations in the HADHA gene lead to low levels of long-chain 3-hydroxyacyl-CoA dehydrogenase, which is part of a protein complex known as mitochondrial trifunctional protein. Long-chain fatty acids from food and body fat cannot be metabolized and processed without sufficient levels of this enzyme.

✓ Inheritance Patterns

LCHAD deficiency is inherited in an autosomal recessive pattern. Parents of a child diagnosed with LCHAD deficiency are unaffected. These individuals are carriers of the condition and have one normal HADHA gene and one abnormal HADHA gene. Each pregnancy between carrier parents has a 25% chance of producing a child affected with LCHAD deficiency, a 50% chance of producing an unaffected carrier child, and a 25% chance of producing a child who is unaffected and is not a carrier.

✓ Treatment

Treatment for LCHAD deficiency involves avoiding long periods of fasting and having frequent meals that are high in carbohydrates and low in fat. Infants should have at least one nighttime feeding, or a late-night snack as they get older, to reduce the time they go without eating. Treatment should begin shortly after birth and is life-long. Some

doctors may also prescribe dietary supplements. Emergency care must be taken if a person with LCHAD deficiency becomes ill and has difficulty keeping food down. This is usually treated in the hospital. People with LCHAD deficiency require treatment through a specialty clinic with experience in treating this disorder. **Parents should always travel with a letter from the child's physician, including treatment guidelines, for any situation that may necessitate hospital admission during an acute illness.**

✓ **Screening Methodology**

Newborn screening for LCHAD deficiency is performed by tandem mass spectrometry (MS/MS). The primary marker for LCHAD deficiency is C16-OH.

✓ **What to do After Receiving Presumptive Positive Long chain 3-hydroxyacyl-CoA dehydrogenase Deficiency Screening Results: MEDICAL EMERGENCY - TAKE THE FOLLOWING IMMEDIATE ACTIONS:**

- 1) Contact family to inform them of the newborn screening result and ascertain clinical status (poor feeding, vomiting, and lethargy).
- 2) Consult with pediatric metabolic specialist.
- 3) Evaluate infant (hepatomegaly, cardiac insufficiency; history of sudden unexpected death in a sibling; maternal liver disease during pregnancy; hypoglycemia). If signs are present or infant is ill, initiate emergency treatment in consultation with metabolic specialist.
- 4) Educate family about signs and symptoms of hypoglycemia and metabolic acidosis.
- 5) Report findings to Kansas Newborn Screening program.
- 6) Call KS Newborn Screening Program at 785-291-3363 with questions about results.
- 7) Report Clinical Findings to Newborn Screening Program at 785-291-3363.

✓ **Confirmation of Diagnosis**

Plasma acylcarnitine and urine organic acid analysis are ordered to determine if the appropriate LCAHDD/TFP profiles are present. Differentiation between both disorders requires further biochemical and molecular genetic testing in cultured fibroblasts derived from a skin biopsy. Mutation analysis of the HADHA gene is also available.

✓ **Communication of Results to Parents**

If a baby has a presumptive positive LCHAD deficiency newborn screening result, additional testing needs to be performed to confirm a diagnosis. In accordance with Kansas Administrative Regulation 28-4-502, it is the responsibility of the attending physician or other birth attendant to obtain repeat specimens when needed to complete the screening process.

If a baby is diagnosed with LCHAD deficiency, the following points should be conveyed to parents:

- **Parents should understand that treatment is lifelong and that compliance with diet and avoidance of fasting and prolonged strenuous exercise is critical.**
- **Although children with LCHAD deficiency are usually healthy, any illness (for example, fever, vomiting or injury) where the child is not eating requires prompt notification of the child's physician.**
- **Parents should be encouraged to keep an individualized written treatment protocol for doctors to utilize in a medical crisis.**
- **The siblings of a baby with LCHAD deficiency have a chance of being affected, even if they haven't had symptoms. Finding out whether other children in the family have LCHAD deficiency is important because early treatment may prevent serious health problems.**
- **People with LCHAD deficiency typically receive follow-up care by a team of professionals that is experienced in treating people with metabolic disorders.**
- **Parents may want to consider a medical emergency bracelet for their child.**

For consultation contact:

Dr. Majed Dasouki
KU Medical Center
Kansas City, Kansas
Office: 913-588-6326

11/24/08



Medium Chain Acyl-CoA Dehydrogenase Deficiency (MCADD) Information for Health Professionals

Medium-chain acyl-CoA dehydrogenase deficiency is a fatty acid oxidation disorder. This enzyme is involved in the mitochondrial beta-oxidation of fatty acids.

➤ Clinical Symptoms

Clinical symptoms usually appear as early as 2 months of age but can occur at any time in life.

Clinical findings may include:

- hypoglycemia
- lethargy
- hypotonia
- persistent vomiting
- failure to thrive
- hepatomegaly, liver failure
- rhabdomyolysis
- Reye syndrome-like episodes
- seizures

Coma and sudden death are possible. Children with MCADD have a significant risk (25%) of death during their first episode of hypoglycemia. The first episode generally occurs following illness or fasting and in the past was sometimes attributed to SIDS.

➤ Incidence

MCADD occurs in greater than 1 in 25,000 births.

➤ Genetics and Inheritance Patterns

ACADM is the only gene known to be associated with medium-chain acyl-coenzyme A dehydrogenase deficiency.

MCADD is inherited in an autosomal recessive pattern. Both parents of an affected child are unaffected, healthy carriers who have one normal *ACADM* gene and one abnormal *ACADM* gene. Each pregnancy by carrier parents has a 25% chance of producing a child affected with MCAD, a 50% chance of having an unaffected carrier child, and a 25% chance of having a child who is unaffected and is not a carrier.

***Siblings of individuals diagnosed with MCADD should be tested for MCADD.

➤ Screening Methodology

In Kansas, newborn screening for fatty acid oxidation defects is performed using tandem mass spectrometry to detect elevated acylcarnitine levels. Early specimen collection (after first 24 hours of age) may enhance the detection of these disorders, as acylcarnitine levels may decrease with infant age. False positive and false negative results are possible with this screening. Some drug therapies, such as valproic acid, benzoic acid, pivalic acid, and medium chain triglyceride oil, can cause false positive results, as can carnitine supplementation.

➤ **Treatment**

Treatment involves avoiding long periods of time without eating and having meals that are high in carbohydrates and low in fats. Infants should have at least one night-time feeding, or a late night snack, to reduce the time they go without eating. Special care must be taken if a person with MCAD deficiency becomes ill and has trouble keeping food down. This is usually treated in the hospital with an intravenous glucose. It is important that children with MCAD deficiency receive specialized management through a clinic with experience in treating this disorder. **Parents should always travel with a letter from the child's physician, including treatment guidelines, for any situation that may necessitate hospital admission during an acute illness.**

➤ **What to do After Receiving Presumptive Positive MCADD Screening Results: MEDICAL EMERGENCY - TAKE THE FOLLOWING IMMEDIATE ACTIONS**

- 1) **Consult with pediatric metabolic specialist.**
- 2) **Evaluate the newborn and refer as appropriate. Such individuals should be evaluated for clinical symptoms including hypoglycemia, lethargy, hypotonia, and dehydration.**
- 3) **Initiate confirmatory/diagnostic tests in consultation with the metabolic specialist.**
- 4) **Call KS Newborn Screening Program at 785-291-3363 with questions about these results.**
- 5) **Report clinical findings to the Newborn Screening Program at 785-291-3363.**

➤ **Confirmation of Diagnosis**

Individuals with a positive screen require immediate clinical evaluation. Prompt confirmatory testing should be performed and the infant should not have periods of fasting during this time. Confirmation of MCAD deficiency can be made through DNA mutation analysis. The diagnosis of MCADD requires an integrated interpretation of various analyses, as well as consideration of the clinical status of the individual. Initial testing should include: plasma acylcarnitine analysis, urine organic acid analysis, and urine acylglycine analysis. Additional skin fibroblast testing or DNA analysis may be done.

➤ **Communication of Results to Parents**

If a baby has a **presumptive positive MCADD** newborn screening result, additional testing needs to be performed to confirm a diagnosis. In accordance with Kansas Administrative Regulation 28-4-502, it is the responsibility of the attending physician or other birth attendant to obtain repeat specimens when needed to complete the screening process.

If a baby is diagnosed with MCADD, the following points should be conveyed to parents:

- ***Treatment is essential to the health of the child and is life-long.***
- ***Episode triggers, such as fasting and illness, need immediate attention.***
- ***If warning signs of the disorder are shown, parents should seek immediate medical care.***
- ***The child should be seen by a pediatric metabolic specialist.***
- ***Genetic counseling may be indicated. A list of counselors and geneticists, whose services are available in Kansas, should be given to the parents if they have not already seen a geneticist.***

For consultation, contact:

Dr. Majed Dasouki
KU Medical Center
Kansas City, KS
Office 913-588-6326

11/24/08



Trifunctional Protein Deficiency Information for Health Professionals

Trifunctional protein deficiency (TFP deficiency) is a fatty acid oxidation disorder. Individuals are lacking or have decreased function of trifunctional protein, leading to an inability to utilize certain dietary fats or fat stored in the body for energy.

✓ Clinical Symptoms

The clinical severity and age of onset may vary among patients with TFP deficiency. Overall, TFP deficiency causes intermittent metabolic crises which usually occur after fasting, long periods of exercise, illness/infection, or physical stress. Symptoms of a metabolic crisis include lethargy, behavioral changes, hypotonia, poor appetite, fever, vomiting, hypoglycemia, and metabolic acidosis. Other clinical problems include cardiomyopathy, hepatomegaly, and rhabdomyolysis. If untreated, metabolic crisis can lead to breathing problems, seizures, coma, and death.

Women carrying a fetus with TFP deficiency are at a significant risk for developing medical problems including HELLP (hypertension, elevated liver enzymes, low platelets) syndrome and AFLP (acute fatty liver of pregnancy).

✓ Incidence

TFP is considered a very rare disorder and occurs in less than 1 in 100,000 births.

✓ Genetics of trifunctional protein deficiency

Mutations in the HADHA and HADHB genes cause TFP deficiency. Mutations result in inadequate levels of the enzyme complex trifunctional protein. This causes an inability to metabolize and process long chain fatty acids leading to metabolic crisis and hypoglycemia. Long-chain fatty acids and partially metabolized fatty acids can also buildup in the body causing hepatomegaly, cardiomyopathy and skeletal myopathy.

✓ How do people inherit trifunctional protein deficiency?

Trifunctional protein deficiency is inherited in an autosomal recessive manner. Parents of an individual with an autosomal recessive condition each carry one copy of the mutated gene, but do not show signs and symptoms of the condition. Each pregnancy between carrier parents has a 25% chance of producing a child affected with TFP deficiency, a 50% chance of producing an unaffected carrier child, and a 25% chance of producing a child who is unaffected and is not a carrier.

✓ Treatment

Immediate diagnosis and treatment of TFP deficiency in the neonatal period is critical to normal brain development and physical growth. Recommended treatment is a lifetime diet that is low in long chain fatty acids and high in carbohydrates. Medium Chain Triglyceride oil is often included in this diet. L-carnitine supplementation may be recommended. During illness, children may need to be admitted for medical care to prevent hypoglycemia and metabolic crisis and fasting should always be avoided.

✓ Screening Methodology

Primary newborn screening for TFP deficiency utilizes tandem mass spectrometry. Individuals with a positive screen will have elevated levels of 3-hydroxypalmitoyl carnitine (C16-OH) and/or elevated levels of C18:1-OH and other long chain acylcarnitines.

✓ What to do After Receiving Presumptive Positive TFP deficiency Screening Results: **MEDICAL EMERGENCY - TAKE THE FOLLOWING IMMEDIATE ACTIONS:**

- 1) The clinician should immediately check on the clinical status of the baby.
- 2) Consultation with a metabolic specialist is essential.
- 3) Call KS Newborn Screening Program at 785-291-3363 with questions about results.
- 4) Report Clinical Findings to Newborn Screening Program at 785-291-3363.
- 5) Same birth siblings (twins, triplets) of infants diagnosed with TFP deficiency should be re-screened; additional testing of these siblings also may be indicated.

✓ Confirmation of Diagnosis

Plasma acylcarnitine and urine organic acid analysis are needed for confirmation. TFP deficiency and long-chain 3-hydroxyacyl-CoA dehydrogenase deficiency (LCHADD) both have the same newborn screening profiles. Differentiation requires biochemical and molecular genetic testing using a skin biopsy.

✓ Communication of Results to Parents

If a baby has a presumptive positive TFP deficiency newborn screening result, additional testing needs to be performed to confirm a diagnosis. In accordance with Kansas Administrative Regulation 28-4-502, it is the responsibility of the attending physician or other birth attendant to obtain repeat specimens when needed to complete the screening process.

If a baby is diagnosed with TFP deficiency, the following points should be conveyed to parents:

- ***Parents should understand that treatment for TFP deficiency will be lifelong.***
- ***Parents should understand that treatment is not curative and that all morbidity cannot be prevented. Long-term management, monitoring, and compliance with treatment recommendations are essential to the child's well-being. A multidisciplinary approach is recommended and should include the following specialties: pediatrics, metabolic disease specialists, and dieticians. A cardiologist, ophthalmologist, and neurologist should also be consulted.***
- ***Genetic counseling services may be indicated. A list of counselors and geneticists, whose services are available in Kansas, should be given to the parents if they have not already seen a geneticist.***

For consultation, contact:

Dr. Majed Dasouki
KU Medical Center
Kansas City, KS
913-588-6326

11/24/08



Very Long-Chain Acyl-CoA Dehydrogenase (VLCAD) Deficiency Information for Healthcare Professionals

Very Long-Chain Acyl-CoA Dehydrogenase (VLCAD) deficiency is a rare, but treatable, cause of cardiomyopathy, fatty liver, skeletal myopathy, pericardial effusion, ventricular arrhythmias, and sudden death. Unrecognized, VLCAD deficiency may be rapidly progressive and fatal secondary to its cardiac involvement. It is classified as a fatty acid oxidation disorder.

✓ Clinical Symptoms

There are three forms of VLCAD deficiency: "Early", "Childhood" and "Adult". Initial signs and symptoms of this disorder occur during infancy or childhood and include hypoglycemia, lethargy, fever, vomiting and muscle weakness. People with an early onset of VLCADD are also at risk of serious complications, such as liver abnormalities and life-threatening heart problems. Fatal infantile encephalopathy may be the only indication of the condition. Symptoms that begin in adolescence or adulthood tend to be milder and generally do not involve heart problems. Episodes of VLCADD can be triggered by periods of fasting, illness, and heavy exercise. Periods of hypoglycemia can happen with or without the other symptoms. Hypoglycemia can cause a child to feel dizzy, clammy, weak, and shaky. If not treated, it can lead to coma, and possibly death.

✓ Incidence

VLCAD deficiency is thought to be a rare disorder. VLCADD is estimated to affect greater than 1 in 75,000 newborns.

✓ Genetics of VLCAD Deficiency

Mutations in the ACADVL gene cause VLCAD deficiency. Mutations in the ACADVL gene lead to inadequate levels of very long-chain acyl-coenzyme A dehydrogenase. Without sufficient amounts of this enzyme, very long-chain fatty acids from food and fats stored in the body are metabolized improperly. As a result, these fats are not converted to energy, leading to characteristic signs and symptoms of this disorder, such as lethargy and low blood sugar.

✓ Inheritance Patterns

VLCAD deficiency is inherited in an autosomal recessive pattern. Parents of a child diagnosed with VLCADD are unaffected. These individuals are carriers of the condition and have one normal ACADVL gene and one abnormal ACADVL gene. Each pregnancy between carrier parents has a 25% chance of producing a child affected with VLCADD, a 50% chance of producing an unaffected carrier child, and a 25% chance of producing a child who is unaffected and is not a carrier.

✓ Treatment

Treatment for VLCAD deficiency involves avoiding long periods of fasting and having frequent meals that are high in carbohydrates and low in fat. Infants should have at least one nighttime feeding, or a late-night snack as they get older, to reduce the time they go without eating. Treatment should begin shortly after birth and is life-long. Some dietary supplements may be prescribed. Emergency care must be taken if a person with VLCAD deficiency becomes ill and has difficulty keeping food down. This is usually treated in the hospital. People with VLCAD deficiency require treatment through a specialty clinic with experience in treating this disorder. **Parents should always travel with a letter from the child's physician, including treatment guidelines, for any situation that may necessitate hospital admission during an acute illness.**

✓ Screening Methodology

Newborn screening for VLCADD is performed by tandem mass spectrometry (MS/MS). The primary marker for VLCAD deficiency is tetradecenoylcarnitine (C14:1).

✓ What to do After Receiving Presumptive Positive Very Long-Chain Acyl-CoA Dehydrogenase Deficiency Screening Results: **MEDICAL EMERGENCY - TAKE THE FOLLOWING IMMEDIATE ACTIONS:**

- 1) Consult with pediatric metabolic specialist.
- 2) Evaluate infant for hepatomegaly, cardiac insufficiency; history of sudden unexpected death in a sibling; maternal liver disease during pregnancy, and hypoglycemia. If signs are present or infant is ill, initiate emergency treatment in consultation with metabolic specialist.
- 3) Educate family about signs and symptoms of hypoglycemia and metabolic acidosis. Parents should be warned that if an infant shows warning signs of the disorder, such as lethargy or vomiting, they should immediately seek medical attention.
- 4) Initiate timely confirmatory/diagnostic testing as recommended by specialist.
- 5) Call KS Newborn Screening Program at 785-291-3363 with questions about results.
- 6) Report Clinical Findings to Newborn Screening Program at 785-291-3363.

✓ Confirmation of Diagnosis

The diagnosis is confirmed by finding increased long chain fatty acids on blood acylcarnitine analysis and on organic acid analysis in urine. Mutation analysis of the ACADVL gene is also available.

✓ Communication of Results to Parents

If a baby has a presumptive positive VLCADD newborn screening result, additional testing needs to be performed to confirm a diagnosis. In accordance with Kansas Administrative Regulation 28-4-502, it is the responsibility of the attending physician or other birth attendant to obtain repeat specimens when needed to complete the screening process.

If a baby is diagnosed with VLCAD deficiency, the following points should be conveyed to parents:

- *Parents should understand that treatment is lifelong and that compliance with diet and avoidance of fasting and prolonged strenuous exercise is critical.*
- *Although children with VLCADD are usually healthy, any illness (for example, fever, vomiting or injury) where the child is not eating requires prompt notification of the child's physician.*
- *Parents should be encouraged to keep an individualized written treatment protocol for doctors to utilize in a medical crisis.*
- *The siblings of a baby with VLCADD have a chance of being affected, even if they haven't had symptoms. Finding out whether other children in the family have VLCADD is important because early treatment may prevent serious health problems.*
- *People with VLCADD typically receive follow-up care by a team of professionals that is experienced in treating people with metabolic disorders.*
- *Parents may want to consider a medical emergency bracelet for their child.*

For consultation contact:

Dr. Majed Dasouki
KU Medical Center
Kansas City, Kansas
Office: 913-588-6326

11/24/08

EXAMPLE OF LETTER TO PARENTS FOR FATTY ACID OXIDATION DISORDERS



Mark Parkinson, Governor
Roderick L. Bremby, Secretary

DEPARTMENT OF HEALTH
AND ENVIRONMENT

www.kdheks.gov

Date

Mother's Name
Address Line 1
Address Line 2

RE: Baby's Name DOB: xx/xx/xxxx

Dear Parent:

Best wishes on the birth of your baby! Shortly after your baby was born, a small blood sample was taken for a test called the Newborn Screen. This test helps parents find out if their baby has certain health problems. A baby can look healthy, but may have a harmful illness that can be found by doing this blood test.

The result of your baby's blood test shows that more testing needs to be done for a fatty acid disorder. ***This does not necessarily mean your child is ill.***

THIS IS WHAT YOU NEED TO DO NOW:

1. Call your baby's doctor. Say that you have received a letter stating that your baby's Newborn Screen test was not normal. Set up a time for your baby to have a second test done as soon as you can.
2. We have < Doctor's Name > listed as your baby's doctor, and we have notified him/her of your baby's test result. If this is NOT your baby's doctor, please call the Newborn Screening Program at 785-296-0109 so we can contact the right doctor.

DO NOT DELAY. YOUR BABY'S HEALTH DEPENDS ON YOU.

If your baby does not have a doctor, or if you have questions about this letter, please call Kansas Newborn Screening at 785-296-0109.

Sincerely,

A handwritten signature in cursive script that reads "Jamey Kendall".

Jamey Kendall BSN, RN
Kansas Newborn Screening
Follow-up Coordinator

A handwritten signature in cursive script that reads "Linda A. Williams".

Linda A. Williams, MT(ASCP)
Kansas Newborn Screening
Follow-up Coordinator



Fatty Acid Disorders Information for Parents

➤ Overview

Fatty acid disorders (also called fatty acid oxidation disorders) are a group of rare, inherited conditions that affect infants from birth. They are caused by enzymes that do not work properly. A number of enzymes are needed to break down fats in the body (a process called fatty acid oxidation). Problems with any of these enzymes can cause a fatty acid oxidation disorder. People with these disorders cannot properly break down fat from either the food they eat or from fat stored in their bodies.

➤ Kansas Newborn Screening for fatty acid disorders

The newborn screening program in the State of Kansas is designed to screen for five different fatty acid disorders. These disorders include:

- Medium chain Acyl-CoA dehydrogenase deficiency (MCADD)
- Very Long chain Acyl-CoA dehydrogenase deficiency (VLCADD)
- Long Chain Hydroxy Acyl-CoA dehydrogenase deficiency (LCHADD)
- Trifunctional Protein Deficiency (TFP)
- Carnitine Uptake Defect (CUD)

➤ Why is newborn screening done for fatty acid disorders?

Newborn screening is done for fatty acid disorders so that babies with these conditions can be diagnosed and treated quickly. Immediate diagnosis and treatment of fatty acid disorders is important for normal development and health. Without prompt diagnosis and treatment, infants with fatty acid disorders will develop varying degrees of developmental delay or mental retardation, medical complications and may even experience death.

➤ Does a positive result from the Kansas Newborn Screening Lab mean that my baby has a fatty acid disorder?

No, not necessarily. Newborn screening identifies babies at increased risk for having one of these disorders. Additional tests will need to be done to determine if the baby actually has a fatty acid disorder.

➤ What are the signs and symptoms of fatty acid disorders?

The age that symptoms start and the types of symptoms that a person has vary. Seemingly well infants and children can suddenly develop low muscle tone, seizures (caused by low blood sugar), liver or heart failure, coma, and death if not treated promptly. The condition may present like sudden infant death syndrome (SIDS).

➤ Is there a cure for fatty acid disorders?

No, there is no cure for fatty acid disorders. However, the outcome is best in infants who are treated early and continue with lifelong treatment. Treatment usually consists of a low fat diet and sometimes medications or supplements. It is most important that children avoid fasting.

➤ Where can I get additional information?

Kansas Newborn Screening at www.kdheks.gov/newborn_screening/info_parents.htm
Save Babies Through Screening Foundation at www.savebabies.org
Screening, Technology and Research in Genetics at www.newbornscreening.info

11/24/08



Carnitine Uptake Defect Information for Parents

➤ Overview

Carnitine uptake defect (CUD) is a condition that affects infants from birth (congenital) and results from an inability of the body to use fat for energy.

➤ What is carnitine uptake defect?

Our body gets energy from the food we eat. Certain chemicals in our bodies, called enzymes, help break down and make energy out of fat in food and fat stored in our body. One enzyme, called carnitine transporter (CT), helps with this process. Carnitine uptake defect occurs if this enzyme is missing or is not working properly.

➤ Why is newborn screening done for carnitine uptake defect?

Newborn screening is done for carnitine uptake defect so that babies with this condition can be diagnosed and treated quickly. Immediate diagnosis and treatment of carnitine uptake defect gives the baby the best opportunity for normal brain development and physical growth. Without prompt diagnosis and treatment, infants with carnitine uptake defect may develop severe health problems, including the possibility of death.

➤ Does a positive result from the Kansas Newborn Screening Lab mean that my baby has carnitine uptake defect?

No, not necessarily. Newborn screening tests for elevated levels of carnitine in a baby's blood. Additional tests will need to be done to determine if a baby has carnitine uptake defect or not.

➤ How common is carnitine uptake defect?

Carnitine uptake defect affects less than 1 in 100,000 infants.

➤ Is carnitine uptake defect inherited?

Carnitine uptake defect is inherited in an autosomal recessive manner. This means that both parents of an affected child are carriers of the condition, but they do not have the disease. Each pregnancy between carrier parents has a 25% chance of producing a child affected with carnitine uptake defect, a 50% chance of producing an unaffected carrier child, and a 25% chance of producing a child who is unaffected and is not a carrier.

➤ What are the signs and symptoms of carnitine uptake defect?

There are two main forms of carnitine uptake defect. In one, symptoms begin in infancy and in the other, symptoms begin during childhood.

In the infant form, babies with carnitine uptake defect will show symptoms between birth and three years of age. Carnitine uptake defect can cause periods of illness, called a metabolic crisis, which are more common if the baby goes for long periods without food or is sick. Symptoms of a metabolic crisis include extreme sleepiness, changes in behavior, a poor appetite, fever, vomiting, diarrhea, and low blood sugar (hypoglycemia). If not treated, a metabolic crisis can lead to breathing problems, swelling of the brain, seizures, coma, and even death. If untreated, babies can also have an enlarged heart or liver, muscle weakness, and anemia.

In the childhood form of carnitine uptake defect, symptoms usually begin when the child is between 1 and 7 years old. Symptoms of this form include an enlarged heart, muscle weakness, and heart failure or death if untreated. Unlike the infant form, these children do not have periods of metabolic crisis.

➤ **How is carnitine uptake defect diagnosed?**

False positive and false negative results are possible with this screening. If carnitine is elevated, additional blood and urine tests will be ordered. Special genetic tests or tests using a skin biopsy might also be needed.

➤ **Is there a cure for carnitine uptake defect?**

No, there is no cure for carnitine uptake defect. However, the outcome is usually excellent in infants who are treated early and continue with lifelong treatment.

➤ **How is carnitine uptake defect treated?**

- Lifelong treatment is required. The primary treatment for carnitine uptake defect is supplementation of L-carnitine. This substance helps the body make energy and get rid of harmful wastes.
- Individuals with carnitine uptake defect need to eat frequently and should not go long periods of time without food. If your child is ill or not eating, they may need to be treated at the hospital.
- A special diet that is low in fat and high in carbohydrates might be recommended.

➤ **Where can I get additional information?**

FOD Family Support Group
2041 Tomahawk
Okemos, MI 48864
(517) 381-1940
www.fodsupport.org

CLIMB (Children Living with Inherited Metabolic Diseases): www.CLIMB.org.uk

United Mitochondrial Disease Foundation: www.umdf.org

11/24/08



Long Chain 3-hydroxyacyl-CoA Dehydrogenase (LCHAD) Deficiency Information for Parents

➤ Overview

Long-chain 3-hydroxyacyl-coenzyme A dehydrogenase (LCHAD) deficiency is an inherited condition which prevents the body from converting certain fats to energy, particularly during periods of fasting. Normally, through a process called fatty acid oxidation, several enzymes work in a step-wise fashion to break down fats and convert them to energy. People with LCHAD deficiency have low or absent levels of an enzyme that metabolizes a group of fats called long-chain fatty acids.

➤ What is LCHAD deficiency?

LCHAD deficiency is a rare metabolic disorder of fatty acid oxidation. People with LCHAD deficiency have problems breaking down certain types of fat into energy for the body. Unrecognized, LCHAD deficiency may be rapidly progressive and fatal with serious complications on the heart.

When our bodies run low on glucose, our bodies turn to fats for energy. This includes times when we are fasting, missing meals, or even during sleep. When the normal LCHAD enzyme is missing or not working well, the body cannot break down fat for energy. Instead, it must rely on glucose. Our bodies have a limited amount of glucose available, though, and when it is used up, the body will try to use fat. This leads to low blood sugar, or hypoglycemia, and to a build up of harmful substances in the blood.

LCHAD deficiency can cause mild effects in some people and more serious health problems in others. Babies and children with LCHAD deficiency usually begin to show symptoms sometime from birth through age two. Symptoms are also more likely to occur when a person with LCHAD deficiency gets sick or has an infection.

✓ Why is newborn screening done for LCHAD deficiency?

Newborn screening is done for LCHAD deficiency so that babies with this condition can be diagnosed quickly, and treatment begun immediately. Untreated LCHAD deficiency can be life-threatening. With immediate and lifelong treatment, most people with LCHAD deficiency live healthy lives with normal growth and development.

➤ Does a positive result from the Kansas Newborn Screening Lab mean that my baby has LCHAD deficiency?

No, not necessarily. Newborn screening measures the baby's level of C16-OH acylcarnitine (and looks for smaller elevations of other long chain acylcarnitines). A markedly elevated C16-OH (3-hydroxypalmit carnitine) level and possibly elevated levels of other acylcarnitines is strongly suggestive of LCHAD deficiency, but additional tests need to be completed for a diagnosis of LCHAD deficiency. **The baby should be immediately evaluated and treated and fasting should be avoided.**

➤ How common is LCHAD deficiency?

LCHAD deficiency occurs in greater than 1 in 75,000 births. Incidence is likely higher in Finland where the carrier rate is 1:175.

➤ How is LCHAD deficiency inherited?

LCHAD deficiency is inherited in an autosomal recessive pattern. Parents of a child diagnosed with LCHAD deficiency do not have the condition. These individuals are, however, carriers of the condition. Carriers have one abnormal copy of the gene for LCHAD and one normal copy. In order to have LCHAD deficiency, a child must inherit two abnormal copies; one from each parent. Each pregnancy between carrier parents has a 25% chance of producing a child affected with LCHAD deficiency, a 50% chance of producing an unaffected carrier child, and a 25% chance of producing a child who is unaffected and is not a carrier.

➤ **What are the signs and symptoms of LCHAD deficiency?**

Signs and symptoms of “early” LCHAD deficiency appear in the newborn period. Symptoms may include extreme sleepiness, weakness, nausea, vomiting, seizures, fever, diarrhea, and behavior changes.

This disorder is sometimes mistaken for Reye syndrome, a severe disorder that may develop in children while they appear to be recovering from viral infections, such as chicken pox or flu.

LCHAD deficiency can cause medical complications during pregnancy for the mother of a child who has LCHAD deficiency. These problems may include: no appetite, vomiting, abdominal pain, and jaundice during the last trimester of pregnancy. If untreated, it can cause liver failure in the mother. This may result in the need for liver transplant or even death. These complications are called HELLP syndrome or maternal acute fatty liver of pregnancy (AFLP). It is not known why women have these complications during pregnancy, or why the problems occur only when the fetus has LCHAD deficiency. Less frequently, these complications may occur in mothers of babies who have other fatty acid oxidation disorders.

➤ **How is LCHAD deficiency diagnosed?**

Elevated C16-OH (3-hydroxypalmit carnitine) and possibly other elevated long-chain acylcarnitines in a newborn screen require immediate medical evaluation. Routine labs and the levels of acylcarnitine in the baby’s blood and organic acids in the urine will be tested to help determine a diagnosis. Additional confirmatory testing may be necessary (this may include a skin biopsy and/or genetic testing).

➤ **Is there a cure for LCHAD deficiency?**

No, there is no cure for LCHAD deficiency. Individuals who are diagnosed and treated before brain, liver, or heart damage occur can develop and grow normally, though some people, even with careful treatment, may experience problems.

➤ **How is LCHAD deficiency treated?**

People with LCHAD deficiency cannot break down fat for energy. They can only use glucose available during and soon after eating. For people without LCHAD deficiency, the body uses fat for energy when glucose is all used up (such as when we have not eaten for a while or when we sleep). When glucose is used up in people with LCHAD deficiency, the body tries to use fat for energy. This leads to low blood sugar (called hypoglycemia), which causes the serious symptoms in LCHAD deficiency. Treatment for LCHAD deficiency is based on avoidance of fasting (avoid going a long time without food) by providing frequent meals and use of intravenous glucose when food cannot be tolerated (such as with a virus, cold, flu, or other common illness). Individuals with LCHAD deficiency should follow a diet high in carbohydrates and protein and low in long chain fatty acids. Some individuals with LCHAD deficiency also take supplements, and most are advised to avoid situations that can trigger symptoms (such as prolonged exercise). Individual treatment plans should be coordinated by a physician with expertise in these syndromes.

➤ **Where can I get additional information?**

FOD Family Support Group
2041 Tomahawk
Okemos, MI 48864
(517) 381-1940
www.fodsupport.org

CLIMB (Children Living with Inherited Metabolic Diseases). www.climb.org.uk

11/24/08



Medium Chain Acyl-CoA Dehydrogenase Deficiency (MCADD) Information for Parents

➤ Overview

Medium chain acyl CoA dehydrogenase deficiency, or 'MCADD,' is a disorder in which your body is unable to breakdown fats to make energy. If left untreated, MCAD deficiency can cause life-threatening illness and may even cause sudden death.

➤ What is MCADD?

The body normally uses sugars from the foods we eat for energy and uses fats as an energy reserve. When all of the sugars in our bodies have been used, we break down fats for energy. One of the enzymes that helps to break down fats is called MCAD. In a child with MCADD, fats cannot be broken down normally because the MCAD enzyme does not work properly. This can result in high levels of partially broken down fats, which are toxic to the brain and nervous system. People with MCADD cannot fast for very long.

➤ Why is newborn screening done for MCADD?

If MCADD is not treated, it can cause serious problems. Up to 25% of babies with MCADD die during their first metabolic crisis. Newborn screening allows babies with MCADD to be detected so that doctors can prevent a crisis from happening.

➤ Does a positive result from the Kansas Newborn Screening Lab mean that my baby has MCADD?

No, not necessarily. Special testing must be done to know if a baby has MCADD.

➤ How common is MCADD?

MCADD occurs in greater than 1 in 25,000 births.

➤ What are the signs and symptoms of MCADD?

A lot of babies with MCADD don't have any symptoms at birth. Symptoms, called metabolic crises, are usually seen for the first time between 2 months and 3 years of age, after children go for long periods of time between eating. Early signs of a metabolic crisis include:

- extreme sleepiness
- irritable mood
- poor appetite
- behavior changes
- fever
- diarrhea
- hypoglycemia or low blood sugar
- vomiting

If the crisis is not treated, more serious problem can occur, such as breathing problems, seizures, brain damage, and coma, which could lead to death. These children may also have acute liver disease and an enlarged liver

➤ **How is MCADD diagnosed?**

The diagnosis of MCAD deficiency can be made by measuring the level of medium chain acylcarnitines on Tandem Mass Spectrometry (MS/MS) analysis of a blood sample. A specific urine organic acid profile, enzyme testing, or mutation analysis of the MCAD gene may also assist in confirming the diagnosis. Diagnostic testing is arranged by metabolic specialists.

➤ **Inheritance**

Medium chain acyl CoA dehydrogenase deficiency is inherited in an autosomal recessive manner. This means that both parents of the affected child are carriers of the condition, but they do not have the disease. Each pregnancy between carrier parents has a 25% chance of producing a child affected with MCAD, a 50% chance of producing an unaffected carrier child, and a 25% chance of producing a child who is unaffected and is not a carrier.

➤ **Is there a cure for MCADD?**

Currently, there is no cure for MCADD, but treatment is very effective.

➤ **How is MCADD treated?**

Treatment for MCADD is very effective. Babies who are treated will grow up to have healthy lives with normal growth and development. Babies with MCADD should follow a strict feeding schedule so they don't go without food for long periods of time. Children should also eat frequent meals and try **not** to go for a long time without eating. When children are ill, they may not feel hungry, but it is important that they still eat and drink fluids so they don't develop hypoglycemia or a metabolic crisis. When they are ill, they should eat foods that are high in carbohydrates, like cereals and pastas. Sometimes medication called L-carnitine is prescribed. In an acute symptomatic episode, IV glucose should be given as soon as possible. Treatment is coordinated by metabolic specialists.

➤ **Where can I find additional information?**

FOD Family Support Group
2041 Tomahawk
Okemos, MI 48864
(517) 381-1940
www.fodsupport.org

CLIMB (Children Living with Inherited Metabolic Diseases). www.climb.org.uk

11/24/08



Trifunctional Protein Deficiency Information for Parents

➤ Overview

Trifunctional protein deficiency, also known as TFP deficiency, is a condition that affects infants from birth (congenital). Babies with TFP deficiency have difficulty turning fat into energy for their body to use.

➤ What is trifunctional protein deficiency?

Our bodies use the food we eat for energy. Certain chemicals in our bodies, called enzymes, help break down the fat in food and fat stored in our body and turn it into energy. One type of enzyme, called trifunctional protein, helps with this process. Trifunctional protein deficiency (TFP deficiency) occurs if this enzyme is missing or is not working properly.

➤ Why is newborn screening done for trifunctional protein deficiency?

Newborn screening is done for TFP deficiency so that babies with this condition can be diagnosed and treated quickly. Immediate diagnosis and treatment of TFP deficiency gives babies the best opportunity for normal growth and development. Without prompt diagnosis and treatment, infants with TFP deficiency are unlikely to survive.

➤ Does a positive result from the Kansas Newborn Screening Lab mean that my baby has trifunctional protein deficiency?

No, not necessarily. Newborn screening tests the level of compounds called long chain acylcarnitines in a baby's blood. Additional tests will need to be done to determine if a baby has TFP deficiency or not.

➤ How common is trifunctional protein deficiency?

Trifunctional protein deficiency is very rare and occurs in less than 1 in 100,000 births.

➤ Is trifunctional protein deficiency inherited?

TFP deficiency is inherited in an autosomal recessive manner. This means that both parents of an affected child are carriers of the condition, but they do not have the disease. Each pregnancy between carrier parents has a 25% chance of producing a child affected with TFP deficiency, a 50% chance of producing an unaffected carrier child, and a 25% chance of producing a child who is unaffected and is not a carrier.

➤ What are the signs and symptoms of trifunctional protein deficiency?

There are three forms of TFP deficiency; early, childhood, and mild.

Early and childhood TFP deficiency can cause periods of illness called metabolic crisis. Symptoms of a metabolic crisis are extreme sleepiness, changes in behavior, weakness, poor appetite, fever, diarrhea, vomiting, hypoglycemia (low blood sugar), and high levels of acidic substances in the blood (metabolic acidosis). If the metabolic crisis is not treated, breathing problems, seizures, coma, and death can occur.

Hypoglycemia or a metabolic crisis generally happen if a baby or child with TFP deficiency goes for a long time without food, is ill, after long periods of exercise, or undergoes physical stress, such as surgery.

Babies with early TFP deficiency usually have many periods of metabolic crisis. They may also have heart problems, breathing problems, and liver problems. Episodes of metabolic crisis can cause learning problems or mental retardation. Children may have periods of muscle weakness and pain. Symptoms of mild TFP deficiency begin between 2 years of age and adulthood. This form does not cause metabolic crisis, but can cause muscle damage. Symptoms of muscle breakdown are aches, cramps, reddish-brown urine color, and breathing problems. Kidney failure can occur if the individual is not treated.

➤ **How is trifunctional protein deficiency diagnosed?**

False positives and false negative results are possible with this screening. If long chain acylcarnitines are elevated, additional confirmatory testing using urine and blood tests will be ordered. A skin biopsy might be necessary for correct diagnosis.

➤ **Is there a cure for trifunctional protein deficiency?**

No, there is no cure for TFP deficiency. Treatment should begin early and continue throughout life to provide the best outcome.

➤ **How is trifunctional protein deficiency treated?**

- Lifelong treatment is required. Your child will need a diet that is low in fat and high in carbohydrates. They should avoid going for long periods of time without eating.
- If the child is ill, they may need treatment at a medical center to prevent a metabolic crisis or hypoglycemia.
- Supplementation of Medium Chain Triglyceride oil and L-carnitine may be prescribed.
- Children should avoid extreme cold and long periods of exercise because this can trigger muscle symptoms.
- Breathing and heart problems can cause death in babies with the early form of TFP deficiency. Treatment can help prolong these babies' lives.

➤ **Where can I get additional information?**

FOD Family Support Group
2041 Tomahawk
Okemos, MI 48864
(517) 381-1940
www.fodsupport.org

CLIMB (Children Living with Inherited Metabolic Diseases). www.CLIMB.org.uk

United Mitochondrial Disease Foundation at www.umdf.org

11/24/08



Very Long-Chain Acyl-CoA Dehydrogenase (VLCAD) Deficiency Information for Parents

➤ Overview

Very Long-Chain Acyl-CoA Dehydrogenase (VLCAD) deficiency is an inherited condition that prevents the body from converting certain fats to energy, particularly during periods of fasting. Normally, through a process called fatty acid oxidation, several enzymes work in a step-wise fashion to break down fats and convert them to energy. People with VLCAD deficiency have low or absent levels of an enzyme that metabolizes a group of fats called very long-chain fatty acids.

➤ What is VLCAD deficiency?

VLCADD is a rare metabolic disorder of fatty acid oxidation. People with VLCADD have problems breaking down certain types of fat into energy for the body. Unrecognized, VLCAD deficiency may be rapidly progressive and fatal because of its effect on the heart.

VLCADD can cause mild effects in some people and more serious health problems in others. Symptoms may start in infancy or not until adulthood. There are three forms of VLCADD: "Early", "Childhood" and "Adult".

➤ Why is newborn screening done for VLCAD deficiency?

Newborn screening is done for VLCADD so that babies with this condition can be diagnosed quickly, and treatment begun immediately. Untreated VLCADD can be life-threatening due to extremely low blood sugar levels, brain damage and heart failure. With immediate and ongoing treatment, many people with VLCADD live healthy lives with typical growth and development.

➤ Does a positive result from the Kansas Newborn Screening Lab mean that my baby has VLCAD deficiency?

No, not necessarily. Newborn screening measures the baby's level of C14: 1 acylcarnitine (and looks for smaller elevations of other long chain acylcarnitines). A markedly elevated C14:1 acylcarnitine (or markedly elevated levels of other acylcarnitines) is strongly suggestive for VLCADD, but additional tests need to be completed for a diagnosis of VLCADD. A less elevated level may mean the baby has VLCADD or it could be a false positive result. Additional tests are necessary regardless of the level of elevation. **The baby should be immediately evaluated and treated and fasting should be avoided.**

➤ How common is VLCAD deficiency?

VLCAD deficiency occurs in greater than 1 in 75,000 infants.

➤ How is VLCAD deficiency inherited?

VLCADD is inherited in an autosomal recessive pattern. Parents of a child diagnosed with VLCADD do not have the condition. These individuals are, however, carriers of the condition. Carriers have one abnormal copy of the gene for VLCADD and one normal copy. In order to have VLCADD, a child must inherit two abnormal copies; one from each parent. Each pregnancy between carrier parents has a 25% chance of producing a child affected with VLCADD, a 50% chance of producing an unaffected carrier child, and a 25% chance of producing a child who is unaffected and is not a carrier.

➤ **What are the signs and symptoms of VLCAD deficiency?**

Signs and symptoms of “early” VLCADD appear in the newborn period. Symptoms may include:

- Lethargy (inactivity or over-sleepiness)
- Irritability
- Problems with feeding (poor appetite)
- Vomiting
- Fever
- Diarrhea
- Hypoglycemia
- Fast, shallow breathing
- Seizures

➤ **How is VLCAD deficiency diagnosed?**

Elevated C14:1 acylcarnitine and/or other elevated long-chain acylcarnitines in a newborn screen require immediate medical evaluation. Routine labs and the levels of acylcarnitine in the baby’s blood and organic acids in the urine will be tested to help determine a diagnosis. Additional confirmatory testing may be necessary (this may include a skin biopsy and/or genetic testing).

➤ **Is there a cure for VLCAD deficiency?**

No, there is no cure for VLCADD. Individuals who are diagnosed and treated before brain, liver, or heart damage occur can develop and grow normally, though some people, even with careful treatment, may experience problems.

➤ **How is VLCAD deficiency treated?**

People with VLCADD cannot break down fat for energy. They can only use glucose available during and soon after eating. For people without VLCADD, the body uses fat for energy when glucose is all used up (such as when we have not eaten for a while or when we sleep). When glucose is used up in people with VLCADD, the body tries to use fat for energy without success. This leads to low blood sugar (called hypoglycemia), which causes the serious symptoms in VLCADD. Treatment for VLCADD is based on avoidance of fasting (avoid going a long time without food) by providing frequent meals and use of intravenous glucose when food cannot be tolerated (such as with a virus, cold, flu, or other common illness). Individuals with VLCADD follow a diet high in carbohydrates and protein and low in long chain fatty acids. Some individuals with VLCADD also take supplements, such as carnitine, and most are advised to avoid situations that can trigger symptoms (such as prolonged exercise).

➤ **Where can I get additional information?**

<http://www.newbornscreening.info/Parents/fattyacid disorders/VLCADD.html>

FOD Family Support Group
2041 Tomahawk
Okemos, MI 48864
(517) 381-1940
www.fodsupport.org

CLIMB (Children Living with Inherited Metabolic Diseases). www.CLIMB.org.uk

11/24/08