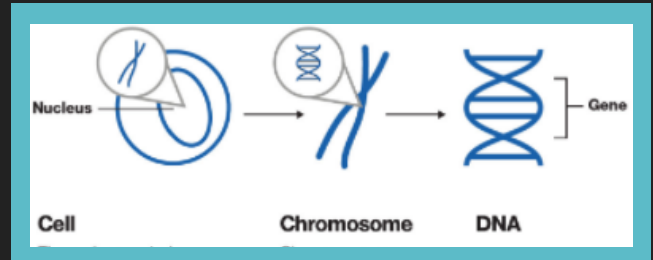


GLOSSARY OF TERMS



TANGO2

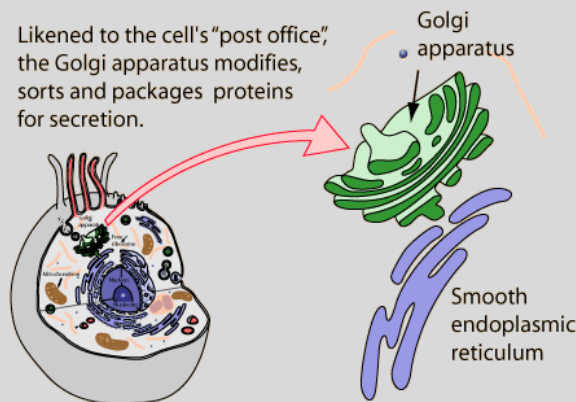
TANGO2 is a gene responsible for performing a specific job in the body which is actually the acronym it stands for -- Transport And Golgi organization.

Golgi

Golgi functions as a factory in which proteins received from the endoplasmic reticulum are processed and sorted for transport to their eventual destinations.

Endoplasmic Reticulum

Endoplasmic reticulum is a collection of tubes that make, package, and transport proteins and fats.



Exons

An exon is a coding region of a gene that contains the information required to encode a protein.

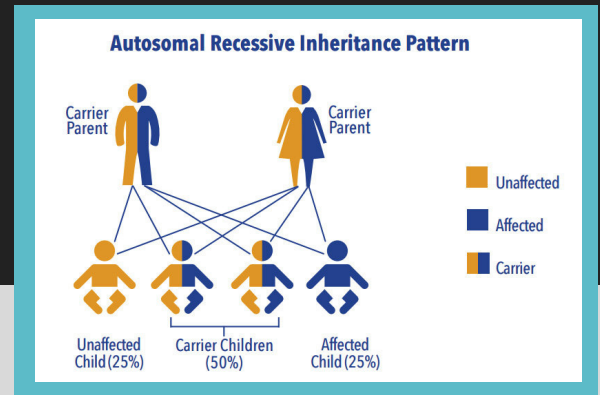
Deletion

A genetic deletion means that a part of a chromosome is missing. A very small piece of a chromosome can contain many different genes. When genes are missing, there may be errors in the development of a baby, since some of the "instructions" are missing.

Misspelling

A misspelling is a change or mutation in a gene.

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Autosomal Recessive

This is a condition inherited from both parents that results from having no functioning copies of a gene.

Mitochondria

Mitochondria are the parts of our cells that generate energy from food that the rest of the cell can use.

Metabolism

Metabolism is all the chemical reactions involved in converting food into energy.

Metabolomics

Metabolomics is the study of small molecules, known as metabolites, within cells, biofluids, tissues or organisms.

Recurrent Metabolic Crises

Our body has an order or a way that it works best to give us energy and keep us healthy. When the TANGO2 gene doesn't work in the body, it disrupts this order and it causes a crisis because we can't utilize this typical way of making energy. We can measure metabolic crisis with lab tests. The body uses up all of its sugar resulting in low blood sugar which leads to hypoglycemia. There can be a build up in lactic acid called lactic acidosis. Lactate and glucose are closely related and so a decrease in one can cause an increase in another. We can also see elevated ammonia called hyperammonemia.

Enzymes

An enzyme is a protein molecule in cells that speeds up chemical reactions in the body, but does not get used up in the process. Therefore it can be used over and over again.

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Fatty Acid Oxidation

During digestion the body breaks down fats into fatty acids which can then be absorbed into the blood. Fatty acids have many important functions in the body, including energy storage. If glucose (a type of sugar) isn't available for energy, the body uses fatty acids to fuel the cells instead.

Membrane Traffic

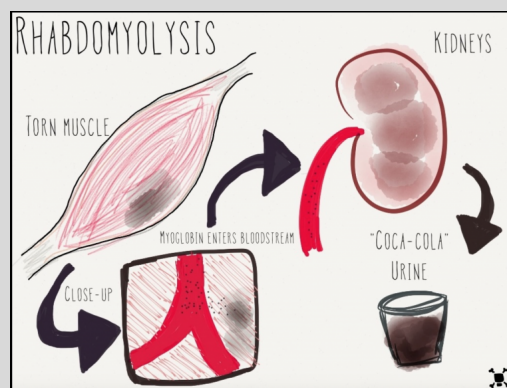
Membrane trafficking is the process by which proteins and other macromolecules are distributed throughout the cell.

Carnitine

Carnitine is a natural substance that the body uses to process fats and produce energy. Carnitine deficiency is when not enough (less than 10%) of the nutrient carnitine is available to cells in the body. This can cause muscle weakness and heart or liver problems.

Rhabdomyolysis

This is the breakdown of muscle. With TANGO2 there can be muscle injury from all the abnormal labs of a metabolic crisis that cause the muscle fibers to die and break down. Muscle that breaks down releases myoglobins which can attack the kidneys. A healthy kidney filters waste, but a kidney that is being attacked can't filter out water and toxins and it can cause changes in urine color and make a child very sick. We measure how much muscle is breaking down by measuring Creatine kinase or CK.



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Myoglobins

Myoglobin is a protein found in heart tissue and other muscles. It is released into the blood after damage to the heart or other muscles. It can be checked with a blood test or a urine test.

Cardiac Arrhythmias

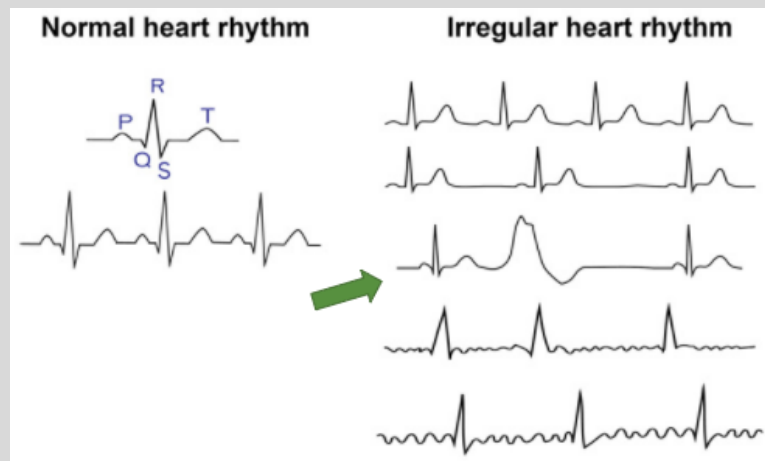
An arrhythmia is any change in heart rhythm. Hearts typically have a very specific wave and the PQRST describes the normal shape of that wave. With arrhythmia related to TANGO2, the most common change is an increase in space between the Q and T part of the wave called QT prolongation. Any change to our normal heart wave is dangerous because it may not snap back into normal rhythm and the heart can stop.

Tachycardia

Tachycardia is an abnormally fast heart rate.

Cardiomyopathy

Cardiomyopathy is when the heart muscle becomes weak and enlarged, which makes it difficult to pump blood through the body.



Myocytes

These are a type of cell found in muscle tissue. They develop from myoblasts to form muscles in a process called myogenesis.

GLOSSARY OF TERMS

Encephalopathy

This is damage to the brain that changes the firing patterns of the mind. Our brain activity is measured in waves. An EEG is an electroencephalogram which measures the electrical impulses of the brain. EEGs are supposed to show minimal peaks but with encephalopathy, there are peaks and lows that don't follow a normal pattern. This is an indication that the brain is not functioning correctly. This often can explain delays and issues in learning.

Biomarker

This is a biological molecule found in blood, other body fluids, or tissues that is a sign of a normal or abnormal process, or of a condition or disease. A biomarker may be used to see how well the body responds to a treatment for a disease or condition.

Pluripotent Stem Cells (iPSC)

These cells are master cells. They are able to make cells from all three basic body layers, so they can potentially produce any cell or tissue the body needs to repair itself. This "master" property is called pluripotency.

Fibroblast

A fibroblast is a cell that forms connective tissue fibers. Skin fibroblasts form skin cells.

Pathophysiology

This is changes in the body associated with a particular disease or injury, or the study of such changes.

CRISPR

CRISPR is a technology that can be used to edit genes.

Name: @NAME@
DOB: @DOB@

Date issued:

EMERGENCY LETTER
TANGO2-Related Metabolic Encephalopathy and Arrhythmias

[ADD NAME] is a [ADD AGE] year old [ADD GENDER] with TANGO2 mutation, which causes a rare genetic disorder. During times of fasting and metabolic stress such as gastroenteritis, respiratory infections, prolonged fasting, or a similar illness, [ADD NAME] can develop the following ACUTE complications:

- ***LIFE THREATENING severe cardiac arrhythmias and cardiac dysfunction. Sudden death has been reported due to fatal ventricular arrhythmias. On ECG, QTc will be prolonged during acute episodes and intermittent Brugada Type I pattern can be seen. In addition, cardiac dysfunction can evolve and develop during the crisis even if systolic function is normal at admission.***
- Individuals with this disease can present with acute metabolic crisis that are typically triggered by illness or decreased oral intake. Symptoms will include lethargy, weakness including difficulty or worsening of baseline gait with some children unable to walk. Muscle pain may also be present. Most but not all with have associated hypoglycemia.
- Profound muscle weakness and ataxia, drooling, difficulty holding up the head, and muscle pain are often seen.
- The hallmark signs of metabolic crisis include rhabdomyolysis with elevated CK and elevated AST/ALT. Hypoglycemia can also be seen but is not always present. The ECG will almost uniformly show evidence of QTc prolongation.
- Chronic symptoms include hypothyroidism, developmental delay, intellectual disability, and slurred speech. Treatment with intravenous fluids/glucose may stabilize the acute process; however because the cardiac systolic function can be depressed, IV fluid rate needs to be managed carefully to avoid pulmonary edema and worsening systolic function.
- In rare patients, pancreatitis and adrenal insufficiency have been seen.

****EMS: – Assess for hypoglycemia, elevated AST/ALT, CK, cardiac rhythm/QTc (by ECG), cardiac function (by echocardiogram) and begin treatment immediately if patient is in crisis. If safe for the patient, please transport patient to a hospital which is equipped to care for this rare genetic condition, or nearest tertiary care hospital.**

EMERGENCY ROOM PHYSICIAN:

1. [ADD NAME] should be triaged as soon as possible upon arrival to the Emergency Room even if the patient does not appear to be ill, because hypoglycemia and life-threatening arrhythmias can occur rapidly.

Labs: STAT fingerstick glucose, STAT Ammonia- should be placed on ice and sent to lab for immediate analysis, CK level, lactate, venous blood gas, Chemistry panel with glucose, amylase, lipase, AST/ALT, and TSH.

ECG: Obtain a standard 12 lead ECG and assess for prolonged QTc (>450msec) and Brugada Type I pattern. If QTc is prolonged >450msec, a second modified Brugada ECG should be obtained (see below) to identify presence of a Brugada Type I pattern in anterior precordial leads (details below).

Start IVF immediately (do not wait on lab results): Please provide IV fluids, D10 with added age-appropriate electrolytes, at 1.5x maintenance rates. Start magnesium replacement to maintain magnesium levels at upper end of normal (typically 2.2-2.3 mg/dL in the United States). Once the echocardiogram is obtained, the rate of IVF may need to be adjusted to avoid worsening function if systolic dysfunction is present.

2. If the patient is in metabolic crisis, perform an echocardiogram to assess systolic function and mitral regurgitation. If systolic dysfunction is present or QTc is >500msec, admit to ICU for continuous monitoring in a hospital that has ability to place the child on ECMO (extracorporeal membrane oxygenator) support if needed. Page

Cardiology/pediatric electrophysiology for risk of ventricular tachycardia and prolonged QTc interval. Do not administer amiodarone, procainamide, or sotalol.

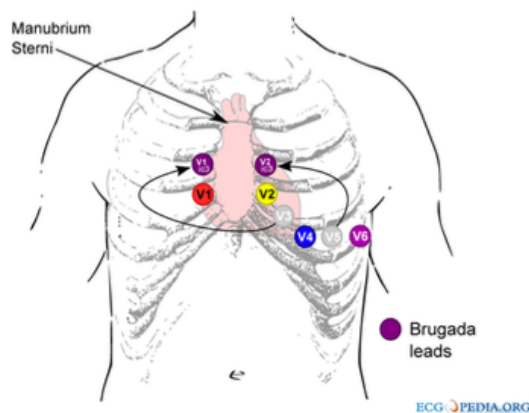
- a. Maintain magnesium IV bolus or continuous gtt to maintain levels at highest normal range.
- b. Place cardiac bedside ECG electrodes in high right precordial position (3rd intercostal space) to observe for fluctuations in Brugada pattern. If present, avoid Lidocaine and all sodium channel blocking agents for any arrhythmia.
- c. If patient begins to have any PVCs, patient needs to be in the ICU. IV magnesium bolus and continuous magnesium should be administered to maintain levels of 2.2-2.3 mg/dL. If any non-sustained or sustained ventricular tachycardia/torsade de pointes, administer isoproterenol bolus: for weight <25kg give 0.5mcg and for >25kg give 1mcg bolus. May be repeated. A pediatric electrophysiologist should be contacted and involved. Patients with persistent ventricular ectopy who are hemodynamically stable can be placed on an isoproterenol drip (doses 0.005-0.01mcg/kg/min to start, titrate to response). Unstable VT should be DC cardioverted with ECMO back up support if necessary. Magnesium bolus should also be given.
- d. Daily ECGs should be obtained during crisis for monitoring of QTc and Brugada pattern. The QTc will typically remain prolonged, may slightly fluctuate, but will begin to decrease back to normal when the patient is recovering from crisis. The patient should not be discharged until the QTc normalizes.
- e. The CK may also rise but can also fall, ultimately will decrease with crisis recovery. The CK may not return entirely to normal for some time but should be trending downward with recovery. Importantly, even if the CK is improving, the patient can still be at risk for cardiac arrhythmias and dysfunction. Thus cardiac status should continue to be monitored, including a repeat echocardiogram while inpatient.

After initial IVF and glucose, focus will need to be on adequate nutrition. Initiate nutrition as soon as possible. If oral intake is not possible, consider placing a nasogastric tube to provide formula supplement such as Nutren 1.5 or Pediasure. If hemodynamically stable, do not keep the patient NPO even if on IVF. If unable to use a nasogastric tube consider administering TPN.

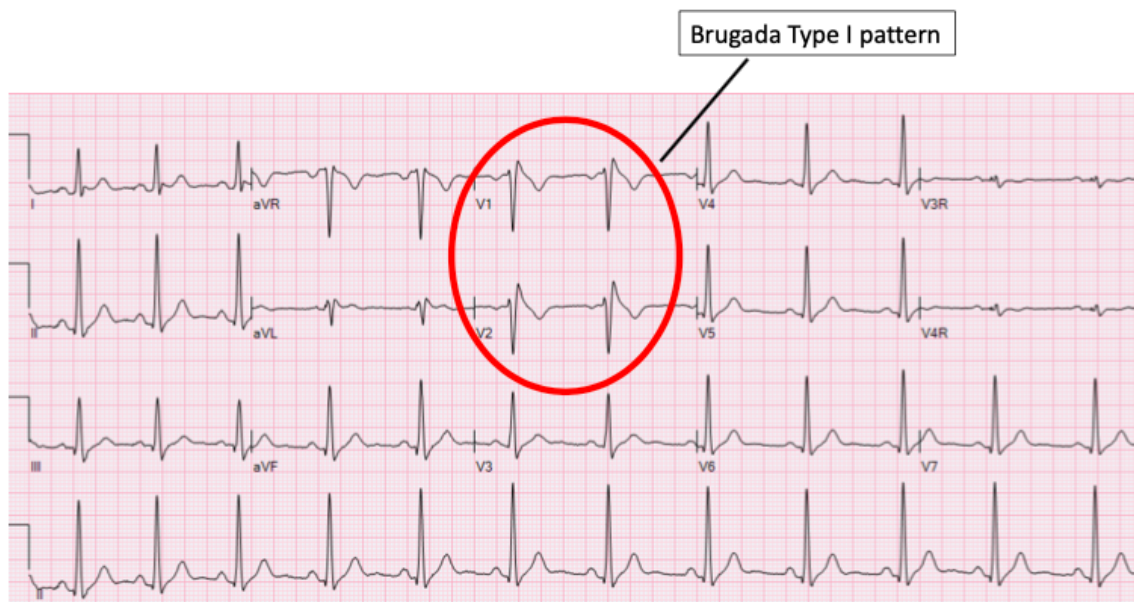
3. **Please call or page genetics/metabolic service to inform of ER or hospital admission. Please page Cardiology service for concerns of high risk of arrhythmia during acute metabolic crises.**

ECG for modified Brugada protocol:

1. For the first ECG please obtain a standard 12 lead ECG which should include right sided leads.
2. For the second modified ECG please place leads in standard position except place the V3R lead one intercostal space directly above V1. Place the V4R lead one intercostal space directly above V2. If you do not have V3R/V4R leads, move the V3 and V4 leads (as shown below) above V1 and V2.



Brugada Type I pattern example (on standard 12 lead ECG) demonstrates anterior (V1 and V2) ST elevation with T wave inversion:



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