Genetics in Special Education Series

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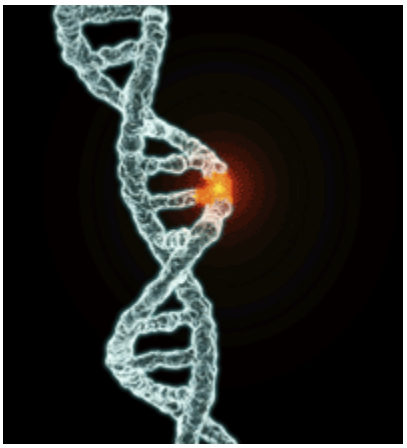

Genetic disorders presented in this issue:

- **Cri du Chat Syndrome**
- **Trimethylaminuria**

Cri du Chat Syndrome

What is cri du chat syndrome?

Cri du chat syndrome - also known as 5p- syndrome and cat cry syndrome - is a rare genetic condition that is caused by the deletion (a missing piece) of genetic material on the small arm (the p arm) of chromosome 5. The cause of this rare chromosomal deletion is unknown.

What are the symptoms of cri du chat syndrome?

The symptoms of cri du chat syndrome vary among individuals. The variability of the clinical symptoms and developmental delays may be related to the size of the deletion of the 5p arm.

The clinical symptoms of cri du chat syndrome usually include a high-pitched cat-like cry, mental retardation, delayed development, distinctive facial features, small head size (microcephaly), widely-spaced eyes (hypertelorism), low birth weight and weak muscle tone (hypotonia) in infancy. The cat-like cry typically becomes less apparent with time.

Most individuals who have cri du chat syndrome have difficulty with language. Half of children learn sufficient verbal skills to communicate. Some individuals learn to use short sentences, while others express themselves with a few basic words, gestures, or sign language.

Other characteristics may include feeding difficulties, delays in walking, hyperactivity, scoliosis, and significant retardation. A small number of children are born with serious organ defects and other life-threatening medical conditions, although most individuals with cri du chat syndrome have a normal life expectancy.

Both children and adults with this syndrome are usually friendly and happy, and enjoy social interaction.

How is cri du chat syndrome diagnosed?

The diagnosis of cri du chat syndrome is generally made in the hospital at birth. A health care provider may note the clinical symptoms associated with the condition. The cat-like cry is the most prominent clinical feature in newborn children and is usually diagnostic for the cri du chat syndrome.

Additionally, analysis of the individual's chromosomes may be performed. The missing portion (deletion) of the short arm of chromosome 5 may be seen on a chromosome analysis. If not, a more detailed type of genetic test called FISH analysis may be needed to reveal the deletion.

What is the treatment for cri du chat syndrome?

No specific treatment is available for this syndrome. Children born with this genetic condition will most likely require ongoing support from a team made up of the parents, therapists, and medical and educational professionals to help the child achieve his or her maximum potential.

With early and consistent educational intervention, as well as physical and language therapy, children with cri du chat syndrome are capable of reaching their fullest potential and can lead full and meaningful lives.

Is cri du chat syndrome inherited?

Most cases of cri du chat syndrome are not inherited. The chromosomal deletion usually occurs as a random event during the formation of reproductive cells (eggs or sperm) or in early fetal development. People with cri du chat typically have no history of the condition in their family.

About 10 percent of people with cri du chat syndrome inherit the chromosome with a deleted segment from an unaffected parent. In these cases, the parent carries a chromosomal rearrangement called a balanced translocation, in which no genetic material is gained or lost. Balanced translocations usually do not cause any medical problems; however, they can become unbalanced as they are passed to the next generation. A deletion in the short arm of chromosome 5 is an example of an unbalanced translocation, which is a chromosomal rearrangement with extra or missing genetic material. Unbalanced translocations can cause birth defects and other health problems such as those seen in cri-du-chat syndrome.

Trimethylaminuria

What is trimethylaminuria?

Trimethylaminuria is a metabolic condition in which an individual is not able to convert trimethylamine into a compound called trimethylamine N-oxide. Trimethylamine is the compound that gives fish the fishy odor. Trimethylamine N-oxide does not smell. Trimethylaminuria, has been around for centuries, but has only gained scientific recognition and support in the past 30 years.

What are the symptoms of trimethylamineuria?

Trimethylamine builds up in the body of patients with trimethylaminuria. The trimethylamine gets released in the person's sweat, urine, reproductive fluids, and breath, giving off a strong fishy odor. Some people with trimethylaminuria have a strong odor all the time, but most have a moderate smell that varies in intensity over time. Other than the strong fishy odor, individuals with this condition typically appear healthy.

The condition seems to be more common in women than men, but scientists don't know why. Scientists suspect that female sex hormones, such as progesterone and/or estrogen, aggravate symptoms. There are several reports that the condition worsens around puberty. In women, symptoms can worsen just before and during menstrual periods, after taking oral contraceptives, and around menopause.

What causes trimethylaminuria?

People with trimethylaminuria have an impaired version of the enzyme flavin-containing monooxygenase 3 (FMO3). This is the enzyme that converts trimethylamine to to trimethylamine N-oxide. FMO3 is produced by the liver and is a member of a family of similar enzymes responsible for metabolizing compounds that contain nitrogen, sulfur, or phosphorous. The enzyme is coded for by the FMO3 gene. Trimethylaminuria may be caused by a variety of genetic changes to the FMO3 gene. Not all of the functions of the FMO3 enzyme are known, so physicians don't know what other symptoms besides odor may be associated with trimethylaminuria.

Is trimethylaminuria inherited?

Yes. Trimethylaminuria is usually inherited in an autosomal recessive fashion, which means that two non-functioning FMO3 genes are usually needed for a person to have symptoms. Both parents of an individual with trimethylaminuria are "carriers" of the condition, in other words, they both carry one copy of an altered gene for FMO3.

Since this condition usually requires two altered genes to cause symptoms, typically neither parent of an individual with trimethylaminuria has any symptoms. Sometimes, "carriers" of one copy of an FMO3 mutation may have mild symptoms of trimethylaminuria or have temporary episodes of fish-like odor. Due to the variability of symptoms people with trimethylaminuria experience, researchers think that different genetic mutations in FMO3 can influence the symptoms of the disease, affecting time of onset and how strong the odor is. They also suspect that stress and diet play a role in triggering symptoms.

How is trimethylaminuria diagnosed?

A urine test is used to diagnose trimethylaminuria. The person's urine is tested to look for higher levels of trimethylamine. Testing can be done by giving choline by mouth followed by urine collection a certain number of times over a 24 hour period. Urine testing should be performed on two separate occasions when the individual is on a non-restricted diet. The test measures the ratio of trimethylamine to trimethylamine N-oxide present in the urine.

A carrier of this condition can be identified by the "TMA challenge" or a "TMA load" test. This involves giving an individual a 600 dmg pill of trimethylamine (TMA). Carriers of trimethylaminuria excrete 20-30 percent of total trimethylamine as the free unmetabolized amine and the rest as trimethylamine N-oxide. Non-carriers excrete less than 13% of the dose as trimethylamine. Gene testing called gene sequencing can be used to look for mutations in the FMO3 gene. Gene testing is currently available only through research laboratories.

How is trimethylaminuria treated?

There is currently no cure for trimethylaminuria. However, it is possible for people with this condition to live normal, healthy lives. The following are some ways a person with trimethylaminuria can lower symptoms of odor:

- Avoiding foods containing trimethylamine and its precursors (choline, lecithin and trimethylamine N-oxide).
- Trimethylamine is present in high levels in milk obtained from wheat-fed cows

- Choline is present in high amounts in:
    - Eggs
    - Liver
    - Kidney
    - Peas
    - Beans
    - Peanuts
    - Soy products
    - Brassicas (brussel sprouts, broccoli, cabbage, and cauliflower)
    - Lecithin and lecithin-containing fish oil supplements
- Trimethylamine N-oxide is present in seafood (fish, cephalopods, crustaceans). Freshwater fish have lower levels of trimethylamine N-oxide.
- Taking low doses of antibiotics to reduce the amount of bacteria in the gut. This suppresses the production of trimethylamine.
- Taking laxatives can decrease intestinal transit time and reduce the amount of trimethylamine produced in the gut.
- Taking supplements to decrease the concentration of free trimethylamine in the urine.
- Activated charcoal taken at a dose of 750mg twice daily for ten days. Copper chlorophyllin taken at a dose of 60mg three times a day after meals for three weeks.
- Using soaps with a moderate pH, between 5.5 and 6.5. Trimethylamine is a strong base (pH 9.8), thus soaps with pH closer to that of normal skin help retain the secreted trimethylamine in a less volatile form that can be removed by washing.
- Taking riboflavin (vitamin B2) supplements to enhance any residual FMO3 enzyme activity. Recommended intake is 30-40mg taken 3-5 times per day with food.
- Avoiding factors that promote sweating, such as exercise, stress, and emotional upsets.

It is important that a person who has trimethylamuinuria follow the treatment advice of their health care provider. They should not attempt to self-administer these treatment approaches. Medications and supplements can have unintended interactions, and dietary restrictions can result in nutritional deficits. Choline is essential for nerve and brain development in fetuses and infants, therefore, pregnant and breast-feeding women should consult with their health care provider before restricting their dietary choline.

People with trimethylaminuria may also find the following to be helpful:

- Behavioral counseling to help with depression and other psychological symptoms.
- Genetic counseling to better understand how they developed the condition and to be aware of the risks of passing this disorder on to the next generation.

Can trimethylaminuria be cured by replacing the enzyme FMO3?

Unfortunately at this time, enzyme replacement therapy with the enzyme FMO3, which when absent, is believed to cause the condition, is not an option in the management of trimethylaminuria.

What laboratories offer testing for trimethylaminuria?

The following laboratories are able to assist in the diagnostic testing of patients who may have trimethylaminuria. Please note that some of these laboratories do not accept direct contact from patients. Therefore, it is recommended that you work with a medical or genetics professional to contact the laboratories for further information.

The laboratories listed below recently began performing clinical diagnostic testing for elevated levels of trimethylamine for patients in the United States.

- University of Colorado Health Science Center
  Dr. Paul Fennessey
  Phone: 303-315-7287
  Contact: Dr. Susan Tjoa
  Phone: 303-315-8175
  susan.tjoa@uchsc.edu

- Monell Chemical Senses Center

  University of Pennsylvania

  Phone: 215-898-4713

  Contact: George Preti, Ph.D.

  preti@monell.org

  Note: This laboratory may have a long waiting list of patients

- Human Biomolecular Research Institute
  5310 Eastgate Mall
  San Diego, CA 92121
  Phone: 858-458-9305
  Fax: 858-458-9311
  E-mail: rhandley@hbri.org Web site: Human BioMolecular Research Institute (HBRI) [hbri.org]
  Web site TM testing: HBRI Trimethylaminuria Web page