Overview of Trimethylaminuria (TMAU)

By Ronald N. Hines, PhD, Professor of Pediatrics and Pharmacology, Medical College of Wisconsin and Associate Director, Children’s Research Institute, Children’s Hospital and Health Systems, Milwaukee, WI

Trimethylaminuria (TMAU), commonly referred to as “fish-odor syndrome”, is caused by the excessive excretion of malodorous trimethylamine (TMA) in the urine, sweat and breath. TMA is derived from the enterobacterial metabolism of dietary precursors such as choline, lecithin, and trimethylamine N-oxide (TMAO; utilized by marine organisms as an osmolyte). Under normal circumstances, TMA uptake leads to extensive first pass metabolism by hepatic flavin-containing monoxygenase 3 (FMO3) and urinary excretion of greater than 95% of the combined TMA/TMAO dietary load as non-odorous TMAO. Primary TMAU results from homozygosity or compound heterozygosity for missense or nonsense FMO3 mutations leading to severely diminished FMO3 oxidative capability. However, other clinical presentations have been reported. A mild and transient TMAU form has been described in females at the onset of menstruation, apparently related to poorly understood hormonal effects on FMO3 function.

Transient TMAU also has been reported in children with the introduction of foods rich in choline, lecithin, or TMAO, apparently due to a delayed onset of hepatic FMO3 expression. FMO3 is essentially absent in fetal and neonatal liver. Expression of the enzyme at levels approximately 10% of adults is seen in most individuals between the neonatal period and one year of age, although there is considerable interindividual variability. Between one year and 11 years, expression increases to 20 to 30% of adult levels and at puberty, a gender-independent gradual increase in expression is observed such that adult levels are observed by 18 years of age. Thus, childhood transient TMAU usually resolves with age.

Although TMAU is generally considered a rare disorder, the true incidence is probably underestimated due to poor clinical awareness and the requirement for specialized technical facilities to confirm the diagnosis. However, TMAU is not benign. Problems with embarrassment and ridicule resulting in low self-esteem, social ostracizing, anxiety and depression are observed, particularly when children begin formal schooling. Thus, early and accurate diagnosis is essential for genetic counseling and long-term management of the disease. Diagnosis in adults is often done with dietary loading of TMA or choline, followed by the assessment of urinary TMA/TMAO by mass spectrometry. However, a diagnostic procedure involving a dietary load of marine fish, such as cod, or meal derived from marine fish, followed by assessment of urinary TMA/TMAO by proton magnetic resonance spectroscopy, is more suitable for pediatric patients. Genetic screens for causative FMO3 mutations also should be performed. Long-term management of the disease currently involves dietary restriction of foods rich in choline, lecithin, and TMAO, although over-restriction of dietary choline in infants and children should be avoided. Foods rich in indoles and glucosinolates, such as cruciferous vegetables, also should be avoided as these compounds are known FMO3 inhibitors. In addition, copper-chlorophyllin tablets can be administered to modulate enterobacteria and absorb excess TMA. Finally, intermittent treatment with broad-spectrum antibiotics such as metronidazole or neomycin has been found effective in suppressing gut flora.
References: