[LITERATURE REVIEW]

A Review of Trimethylaminuria
(Fish Odor Syndrome)

[a]JEFFREY MESSENGER, MD; [b]SHANE CLARK, MD; [b]SUSAN MASSICK, MD; [b]MARK BECHTEL, MD
[a]College of Medicine, The Ohio State University, Columbus, Ohio; [b]Division of Dermatology, The Ohio State University, Columbus, Ohio

ABSTRACT

Trimethylaminuria, better known as fish odor syndrome, is a psychologically disabling condition in which a patient emits a foul odor, which resembles that of rotting fish. The disorder is most commonly caused by an inherited deficiency in flavin monooxygenase 3, the vital enzyme for the metabolism of trimethylamine, which is the compound responsible for the unpleasant odor. The condition is uncommon, but there has been recent research to suggest that the diagnosis may often be overlooked. Moreover, it is important to be cognizant of this condition because there are reliable diagnostic tests and the disorder can be devastating from a psychosocial perspective. While there is no cure, many simple treatment options exist that may drastically improve the quality of life of these patients. This article will review the literature with an emphasis on the psychosocial impact and treatment options. (*J Clin Aesthet Dermatol.* 2013;6(11):45–48.)

Trimethylaminuria, or fish odor syndrome (FOS), is a condition characterized by the presence of trimethylamine (TMA)—a tertiary amine whose odor is described as resembling that of rotting fish—in the urine, sweat, and expired air. The cause of the syndrome is rooted in the dysfunctional metabolism of TMA,[1] which is normally oxidized by flavin monooxygenase 3 (FMO3) into non-odorous trimethylamine-N-oxide (TMAO).[2,3] In 1970, Humbert at el[4] published the first case report of FOS; however, William Shakespeare's description of a slave who smelled like fish in *The Tempest* may indicate that the condition was recognized much earlier. It is difficult to estimate the true prevalence of this syndrome, but a decade ago there were more than 200 cases described, which was considered an underestimate at that time.[5] More recently, it has been shown that undiagnosed cases of trimethylaminuria may be fairly common among patients suffering from idiopathic malodor production,[6] which supports the thought that this disorder is under recognized. Genetic studies have estimated the incidence of heterozygous carriers to range from 0.5 to 11 percent depending on the ethnicity examined.[7,8] Cases have been reported from nearly all parts of the world and in both sexes, although it seems that females, particularly those of African descent, may be over-represented.[5,6] In childhood or early adulthood, afflicted individuals usually complain of body odor and/or halitosis and seek care from pediatricians, family doctors, or specialists, such as dermatologists. The odor may not always be pungent as patients may have learned to minimize the smell through simple measures, such as frequent bathing, so it is imperative that healthcare providers be cognizant of this disorder. While not directly life threatening, FOS has a significant psychosocial impact that should not be overlooked.[9–11] This article provides a brief review of the literature with an emphasis on the psychosocial impact of the condition and treatment options.

ETIOLOGY

Most patients with FOS are eventually diagnosed with primary trimethylaminuria, which is caused by a deficiency in FMO3 that is inherited in an autosomal recessive fashion.[1] Under normal circumstances, dietary TMAO and other TMA precursors, such as choline, are ingested and then reduced to TMA by colonic bacteria. The TMA passively diffuses across cell membranes[12–14] and enters the enterohepatic circulation where it is removed by the liver. It is in the liver that FMO3 normally oxidizes TMA into odorless TMAO[2,3]; however, those afflicted with this condition lack adequate functional FMO3 and therefore experience an excess of foul-smelling TMA. While primary trimethylaminuria accounts for the majority of cases, there also exists secondary or acquired trimethylaminuria where FMO3 may still retain

DISCLOSURE: The authors report no relevant conflicts of interest.
ADDRESS CORRESPONDENCE TO: Mark Bechtel, MD; E-mail: Mark.Bechtel@osumc.edu

varying degrees of functionality. Secondary cases may occur in the setting of excess precursor burden as occurred after therapeutic administration of choline for the treatment of Huntington's chorea[15] and Alzheimer's disease.[16] Hepatic disease may serve as another cause as demonstrated in cases of apparent viral hepatitis[5,17] and in instances of portosystemic shunting and markedly impaired hepatocellular function.[18,19] Further, trimethylaminuria has been reported in chronic kidney disease, presumably secondary to bacterial overgrowth in the large intestine.[20] FOS has also been described transiently in early childhood[21,22] when FMO3 levels are minimal and in the perimenstrual period,[10,23–26] when steroid hormones may have caused a reduction in FMO3 expression.[27]

PSYCHOSOCIAL IMPACT

Regardless of the etiology, FOS is often associated with significant psychosocial disturbances, which must be considered when developing a treatment plan. Patients with FOS are often ridiculed and suffer from low self-esteem. Withdrawing from their peers, they become lonely, which may negatively impact their academic performance.[28] Anxiety can also be an issue for these patients, especially if they are unable to detect their odor.[10] Patients also admit to experiencing shame and distress over their condition, and cases of attempted suicide have been noted.[9–11,29] Ayesh et al[10] studied 11 patients with FOS and noted depression, paranoia, career disadvantages, and failure to engage in sustained relationships with members of the opposite sex in addition to the aforementioned psychosocial issues. Interestingly, FMO3 is also responsible for the metabolism of other endogenous amines, such as tyramine, which are present in the brain.[30] It is conceivable that the disordered metabolism of these endogenous amines could cause or at least contribute to the mood disorders described in this patient population. At any rate, there is an apparent benefit in providing the patient with a diagnosis as they are then able to research the disorder for themselves, seek help from support foundations, and discuss the disorder with family and friends.[9,31]

DIAGNOSTIC TESTING

The diagnosis, which often eludes practitioners for years, is made on the basis of the clinical presentation and urinalysis. Urine can be analyzed for the concentration of both TMA and TMAO, and the results may be given as an oxidizing ratio based on the formula TMAO/(TMAO+TMA) x 100%.[32] A ratio of less than 84 percent should be observed in an affected individual with two FMO3 inactivating mutations.[33] Conversely, individuals not afflicted with FOS should have a ratio of greater than 92 percent.[32] Many patients, in an attempt to reduce their odor, may have empirically tailored their diet to exclude TMA precursors, which could cause a false-negative test result. Therefore, it is critical to ensure that adequate substrate has been ingested in order to allow for maximum sensitivity, which may be accomplished by making use of the Nijmegen protocol[33] or loading the patient with a 300g marine fish meal.[32] Genetic testing is available and Shephard et al[27] recommend molecular analysis for any patient excreting greater than 10 percent of total TMA as the free amine.

TREATMENT CONSIDERATIONS

Once the diagnosis has been established, there are a number of potentially helpful treatment options; however, no single regimen seems universally efficacious.[34] Furthermore, no systematic study has been performed to test the various recommendations.[32] An easy first step for the patient might be to wash frequently with an acidic soap (pH 5.5–6.5)[35] and launder clothes on a regular basis.[33] It will also be helpful to inform the patient that the malodor will intensify with fever, stress, exercise, or any other cause of increased perspiration.[36]

Another logical solution to FOS is to exclude or reduce TMAO, a TMA precursor, from the diet, which is found in high concentration in marine fish. While deprivation of marine fish is unlikely to have major repercussions, the same does not apply to choline, another TMA precursor. Choline deficiency may result in hepatocellular injury, neurological disease, and even a predisposition to cancer.[37–41] Notably, pregnant women have an increased choline requirement so restricting intake may be even less desirable in this demographic.[42,43] Foods with high concentrations of choline include eggs, mustard seeds, chicken and beef liver, and raw soybeans.[44] Busby et al[45] have developed diets with defined amounts of choline that patients may find useful. Also, limiting the ingestion of Brussels sprouts, among other vegetables, may be beneficial, as they may inhibit the enzyme FMO3.[46,47] Carnitine and glycine betaine are two other substrates that may theoretically produce a fishy odor[36]; however, whether restricting the ingestion of these substances is of benefit in FOS is unknown.[32] It would behoove any patient considering dietary restriction as a treatment for FOS to consult a professional dietitian to ensure that all essential nutrients are accounted for prior to beginning a new diet. If restriction is not a viable option, a theoretical benefit may be derived from supplementation with riboflavin since FMO3 has a flavin cofactor; however, this has not been substantiated with any clinical study.[32]

Yamazaki et al[48] studied the ability of sequestering agents to improve FOS as determined by the oxidizing ratio in the urine. In theory, the agents would act to reduce the load of TMA that FMO3 would need to metabolize by binding precursor amines in the colon. Oral activated charcoal was given to two subjects with ratios less than 90 percent and copper chlorophyllin was given to three subjects with similarly low ratios. After the intervention, all of the subjects showed an elevation in their oxidizing ratios to greater than 90 percent. Another treatment, which exerts its effect in the gastrointestinal tract, is the use of antimicrobials. Short courses of oral neomycin, metronidazole, and amoxicillin have been reported to be useful in some cases.[36,49,50] The mechanism involves the destruction of gut bacteria, which are responsible for the reduction of TMAO into TMA. However, antimicrobial therapy only moderately alleviated the foul odor[36] and presents a number of possible side effects

if used chronically, so this modality is best suited for transient cases or in instances where bacterial overgrowth is thought to be a major factor in the pathogenesis of FOS. Lactulose, which also acts in the alimentary canal, is another therapy that has demonstrated an ability to decrease urinary TMA.[51] Lastly, it is of great importance to offer a referral to psychiatric counseling and to screen regularly for depression and suicidal ideation.

DISCUSSION

TMAU is most commonly an inherited disorder that is characterized by an unpleasant odor similar to that of rotting fish. The disease was once considered quite rare, but recent research has demonstrated that the condition may be more prevalent than historically appreciated.[6] The disease itself is not life threatening, but it significantly diminishes the quality of patients' lives, and has even been associated with suicide attempts.[9–11,29] While there is no definitive cure at present, it is worth pursuing this diagnosis if clinically indicated as there are reliable diagnostic tests and efficacious treatment options. The diagnosis can be established cost effectively by determining the oxidizing ratio of a urine specimen[32] or by molecular means which are utilized in genetic testing.[27] There are many options to reduce the severity of the condition, which range from simple lifestyle changes, such as washing with acidic soap[35] and eating a choline-deficient diet to utilizing antibiotics[36,49,50] and sequestering agents.[48] TMAU is devastating psychosocially and usually remains undiagnosed for a long period of time; therefore, simply providing those afflicted with the diagnosis can be therapeutic. A low threshold of suspicion for TMAU should be maintained by clinicians as this condition has a devastating effect on quality of life, reliable methods of diagnosis, and myriad treatment options.

REFERENCES

1. Treacy EP, Akerman BR, Chow LM, et al. Mutations of the flavin-containing monooxygenase gene (FMO3) cause trimethylaminuria, a defect in detoxification. *Hum Mol Genet.* 1998;7:839–845.
2. Ziegler DM. Flavin-containing monooxygenases: catalytic mechanism and substrate specificities. *Drug Metab Rev.* 1988;19:1–32.
3. Jones KC, Ballou DP. Reactions of the 4a-hydroperoxide of liver microsomal flavin-containing monooxygenase with nucleophilic and electrophilic substrates. *J Biol Chem.* 1986;261:2553–2559.
4. Humbert JA, Hammond KB, Hathaway WE, et al. Trimethylaminuria: the fish-odour syndrome. *Lancet.* 1970;2:770–771.
5. Mitchell SC, Smith RL. Trimethylaminuria: the fish malodor syndrome. *Drug Metab Dispos.* 2001;29:517–521.
6. Wise PM, Eades J, Tjoa S, et al. Individuals reporting idiopathic malodor production: demographics and incidence of trimethylaminuria. *Am J Med.* 2011;124:1058–1063.
7. Al-Waiz M, Ayesh R, Mitchell SC, et al. A genetic polymorphism of the N-oxidation of trimethylamine in humans. *Clin Pharmacol Ther.* 1987;42:588–594.
8. Mitchell SC, Zhang AQ, Barrett T, et al. Studies on the discontinuous N-oxidation of trimethylamine among Jordanian, Ecuadorian and New Guinean populations. *Pharmacogenetics.* 1997;7:45–50.
9. Mountain H, Brisbane JM, Hooper AJ, et al. Trimethylaminuria (fish malodour syndrome): a "benign" genetic condition with major psychosocial sequelae. *Med J Aust.* 2008;189:468.
10. Ayesh R, Mitchell SC, Zang A, Smith RL. The fish odour syndrome: biochemical, familial, and clinical aspects. *BMJ.* 1993;307:655–657.
11. Todd WA. Psychosocial problems as the major complication of an adolescent with trimethylaminuria. *J Pediatr.* 1979;94: 936–937.
12. Asatoor AM, Simenhoff ML. The origin of urinary dimethylamine. *Biochim Biophys Acta.* 1965;111:384–392.
13. Zeisel SH, Wishnok JS, Blusztajn JK. Formation of methylamines from ingested choline and lecithin. *J Pharmacol Exp Ther.* 1983;225:320–324.
14. Zeisel SH, daCosta KA, Youssef M, Hensey S. Conversion of dietary choline to trimethylamine and dimethylamine in rats: dose-dependent relationship. *J Nutr.* 1989;119:800–804.
15. Growdon JH, Cohen EL, Wurtman RJ. Huntington's disease: clinical and chemical effects of choline administration. *Ann Neurol.* 1977;1:418–422.
16. Etienne P, Gauthier S, Johnson G, et al. Clinical effects of choline in Alzheimer's disease. *Lancet.* 1978;1:508–509.
17. Ruocco V, Florio M, Filioli FG, et al. An unusual case of trimethylaminuria. *Br J Dermatol.* 1989;120:459–461.
18. Marks R, Dudley F, Wan A. Trimethylamine metabolism in liver disease. *Lancet.* 1978;1:1106–1107.
19. Mitchell S, Ayesh R, Barrett T, Smith R. Trimethylamine and foetor hepaticus. *Scand J Gastroenterol.* 1999;34:524–528.
20. Rehman HU. Fish odor syndrome. *Postgrad Med J.* 1999;75: 451–452.
21. Blumenthal I, Lealman GT, Franklyn PP. Fracture of the femur, fish odour, and copper deficiency in a preterm infant. *Arch Dis Child.* 1980;55:229–231.
22. Mayatepek E, Kohlmüller D. Transient trimethylaminuria in childhood. *Acta Paediatr.* 1998;87:1205–1207.
23. Cashman JR, Camp K, Fakharzadeh SS, et al. Biochemical and clinical aspects of the human flavin-containing monooxygenase form 3 (FMO3) related to trimethylaminuria. *Curr Drug Metab.* 2003;4:151–170.
24. Zhang AQ, Mitchell SC, Smith RL. Exacerbation of symptoms of fish-odour syndrome during menstruation. *Lancet.* 1996;348:1740–1741.
25. Mitchell SC, Smith RL. A physiological role for flavin-containing monooxygenase (FMO3) in humans? *Xenobiotica*. 2010;40:301–305.
26. Shimizu M, Cashman JR, Yamazaki H. Transient trimethylaminuria related to menstruation. *BMC Med Genet.* 2007;8:2.
27. Shephard EA, Treacy EP, Phillips IR. Clinical utility gene card for: trimethylaminuria. *Eur J Hum Genet*. 2012;20(3). Epub 2011 Nov 30.
28. Walker V. The fish odour syndrome. *BMJ.* 1993;307:639–640.
29. Christodoulou J. Trimethylaminuria: an under-recognised and

socially debilitating metabolic disorder. *J Paediatr Child Health.* Epub 31 January 2011.
30. Lin J, Cashman JR. Detoxication of tyramine by the flavin-containing monooxygenase: stereoselective formation of the trans oxime. *Chem Res Toxicol.* 1997;10:842–852.
31. Arseculeratne G, Wong AK, Goudie DR, Ferguson J. Trimethylaminuria (fish-odor syndrome): a case report. *Arch Dermatol.* 2007;143:81–84.
32. Mackay RJ, McEntyre CJ, Henderson C, et al. Trimethylaminuria: causes and diagnosis of a socially distressing condition. *Clin Biochem Rev.* 2011;31:33–43.
33. Wevers RA, Engelke UF. Trimethylaminuria. In: Blau N, ed. *Laboratory Guide to the Methods in Biochemical Genetics.* New York: Springer-Verlag; 2008; 781–792.
34. Danks DM, Hammond J, Schlesinger P, et al. Trimethylaminuria: diet does not always control the fishy odor. *N Engl J Med.* 1976;295:962.
35. Wilcken J. Acid soaps in the fish odour syndrome. *BMJ.* 1993;307:1497.
36. Chalmers RA, Bain MD, Michelakakis H, et al. Diagnosis and management of trimethylaminuria (FMO3 deficiency) in children. *J Inherit Metab Dis.* 2006;29:162–172.
37. Zeisel SH, Albright CD, Shin OH, et al. Choline deficiency selects for resistance to p53-independent apoptosis and causes tumorigenic transformation of rat hepatocytes. *Carcinogenesis.* 1997;18:731–738.
38. Zeisel SH. Choline, an essential nutrient for humans. *Nutrition.* 2000;16:669–671.
39. Buchman AL, Dublin MD, Moukarzel AA, et al. Choline deficiency: a cause of hepatic steatosis during parenteral nutrition that can be reversed with intravenous choline supplementation. *Hepatology.* 1995;22:1399–1403.
40. Grön G, Brandenburg I, Wunderlich AP, Riepe MW. Inhibition of hippocampal function in mild cognitive impairment: targeting the cholinergic hypothesis. *Neurobiol Aging.* 2006;27:78–87.
41. Holmes-McNary MQ, Loy R, Mar M-H, et al. Apoptosis is induced by choline deficiency in fetal brain and in PC12 cells. *Brain Res Dev Brain Res.* 1997;101:9–16.
42. Sweiry JH, Yudilevich DL. Characterization of choline transport at maternal and fetal interfaces of the perfused guinea-pig placenta. *J Physiol.* 1985;366:251–266.
43. Sweiry JH, Page KR, Dacke CG, et al. Evidence of saturable uptake mechanisms at maternal and fetal sides of the perfused human placenta by rapid paired-tracer dilution: studies with calcium and choline. *J Dev Physiol.* 1986;8:435–445.
44. Zeisel SH, Mar M-H, Howe JC, Holden JM. Concentrations of choline-containing compounds and betaine in common foods. *J Nutr.* 2003;133:1302–1307.
45. Busby MG, Fischer L, DaCosta K, et al. Choline- and betaine-define diets for use in clinical research and for the management of trimethylaminuria. *J Am Diet Assoc.* 2004;104:1836–1845.
46. Cashman JR, Xiong Y, Lin J, et al. *In vitro* and *in vivo* inhibition of human flavin-containing monooxygenase form 3 (FMO3) in the presence of dietary indoles. *Biochem Pharmacol.* 1999;58:1047–1055.
47. Fenwick GR, Butler EJ, Brewster MA. Are brassica vegetables aggravating factors in trimethylaminuria (fish odour syndrome)? *Lancet.* 1983;2:916.
48. Yamazaki H, Fujieda M, Togashi M, et al. Effects of the dietary supplements, activated charcoal and copper chlorophyllin, on urinary excretion of trimethylamine in Japanese trimethylaminuria patients. *Life Sci.* 2004;74:2739–2747.
49. Treacy E, Johnson D, Pitt JJ, Danks DM. Trimethylaminuria, fish odour syndrome: a new method of detection and response to treatment with metronidazole. *J Inherit Metab Dis.* 1995;18:306–312.
50. Fraser-Andrews EA, Manning NJ, Ashton GH, et al. Fish odour syndrome with features of both primary and secondary trimethylaminuria. *Clin Exp Dermatol.* 2003;28:203–205.
51. Pike MG, King GS, Pettit BR, et al. Lactulose in trimethylaminuria, the fish-odour syndrome. *Helv Paedriatr Acta.* 1989;43:345–348.