Trimethylaminuria (Fish-Odor Syndrome)

A Case Report

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Background: Trimethylaminuria (fish-odor syndrome) is a rare metabolic disorder characterized by a body malodor similar to that of decaying fish. The condition results from mutations affecting the flavin-containing monooxygenase 3 (FMO3) gene. Affected individuals may exhibit a variety of psychosocial phenomena. A high index of suspicion for this disorder needs to be maintained when treating individuals presenting with a history of real or perceived body odor.

Observation: We evaluated a 41-year-old man who presented with a long medical history of a fishy body odor. Results from biochemical investigations confirmed a diagnosis of primary trimethylaminuria, and results of molecular genetic studies revealed homozygosity for a mutation on exon 4 of the FMO3 gene, FMO3/P153L (c.458C→T). The patient found that information he subsequently obtained about his condition on the Internet and discussion with friends and family members to be the most useful therapeutic approach.

Conclusions: Trimethylaminuria is a rare metabolic disorder. Psychological accompaniments are recognized as major sources of distress to affected individuals. We discuss the features of this syndrome and highlight the importance of counseling and support in the treatment of such patients.

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Trimethylaminuria is a relatively rare condition, characterized by a body odor similar to that of decaying fish.

Report of a Case

A 41-year-old man presented with history of a fishy odor that had been commented on by friends since he was 13 years old. Neither the patient nor his family members has been able to detect this malodor, which was a cause of considerable social embarrassment to the patient. He had had topical antiperspirants without much benefit. His medical history revealed a minor head injury, arthroscopy and meniscectomy, corneal foreign-body removal, reflux esophagitis, a duodenal ulcer, and panic attacks, the latter treated with propranolol hydrochloride. The family medical history revealed parental consanguinity, a brother who thought he had the same condition as our patient, and an unaffected sister. No malodor or skin abnormalities were detected at the initial examination but, because the clinical suspicion was that of trimethylaminuria (fish-odor syndrome), he was evaluated for that disorder. While on his normal diet, the urinary trimethylamine (TMA) level was 14.7 µmol/mmol of creatinine (reference range, 1.5-11.0 µmol/mmol). The TMA-N-oxide level was 34 µmol/mmol of creatinine (reference range, 17-147 µmol/mmol), and the TMA/TMA-oxidase ratio was 0.43 (reference range, 0.01-0.21). The significantly high excretion of TMA with a raised TMA/TMA-oxidase ratio was consistent with the diagnosis of primary trimethylaminuria. The patient was referred to a dietitian for advice on foods that contain low amounts of choline and lecithin. Two months later, his TMA level was 9.6 µmol/mmol of creatinine (reference range, 1.5-11.0 µmol/mmol), which reflected successful dietary modification. However, his urinary TMA level was elevated at 102.8 µmol/mmol of creatinine; the TMA-N-oxide level was 263.4 µmol/mmol of creatinine, and the TMA/TMA-N-oxide ratio was 0.39 when investigations were subsequently repeated, possibly a reflection of dietary relaxation. He received a trial dosage of 500 mg of oral metronidazole twice daily for 10 days,
Body malodor is recognized as a distressing symptom for patients and poses a treatment challenge for clinicians. Several descriptive terms have been used in relation to body odor syndromes; dermatologists may experience the rancid odor of erythroderma, the cheesy smell of trichophytion, and the fishy odor of pemphigus.

Trimethylaminuria, a rare metabolic disorder, results from a defect in the hepatic microsomal oxidase enzyme system, which metabolizes TMA. The condition, characterized by an odor similar to that of decaying fish, is inherited as an autosomal recessive trait and was first described by Humbert et al in 1970. The rarity of the condition, which did help to some degree in reducing the degree of odor, has been the fact that he was able to communicate with family members and friends about the condition, which he subsequently read about on the Internet. Molecular genetic studies confirmed homozygosity for a mutation in exon 4 of the flavin-containing monooxygenase 3 (FMO3) gene, FMO3/P153L (c.458C→T), a mutation known to be associated with complete loss of FMO3 enzyme activity.

Figure. Metabolism of dietary precursors of trimethylamine (TMA) (eg, choline, lecithin, and carnitine) lead to production of a volatile tertiary amine, and patients with trimethylaminuria excrete excessive amounts of the free amine as a result of defective hepatic N-oxidation of TMA.

which did help to some degree in reducing the degree of odor. The most useful therapeutic approach, however, had been the fact that he was able to communicate with family members and friends about the condition, which he subsequently read about on the Internet. Molecular genetic studies confirmed homozygosity for a mutation in exon 4 of the flavin-containing monooxygenase 3 (FMO3) gene, FMO3/P153L (c.458C→T), a mutation known to be associated with complete loss of FMO3 enzyme activity.

COMMENT

Early confirmation of the diagnosis is important when the condition is suspected owing to medical history or clinical examination. Local causes of altered olfactory perception need to be excluded because trimethylaminuria has been reported in association with dysosmia.

Fishy odors may be perceived by individuals with cacosmia (ie, abnormal odors perceived by persons exposed to neutral odors). The main confirmatory test is the estimation of free urinary TMA excretion. The levels of trimethylamine as well as of TMA-oxidase could be assessed while patients are eating a normal diet as well as when they are eating a restrictive diet. Choline loading has been used as an aid to diagnosis in patients with trimethylaminuria. Oral challenge with TMA is helpful as far as identifying possible carriers is concerned. The genotypic contribution to phenotypic expression in trimethylaminuria has been studied using the

tential to form the carcinogen N-nitrosodimethylamine. The TMA N-oxidation is catalyzed by an FMO. It is recognized that a process of isomor switching (from FMO1 to FMO3 occurs, FMO1 being the predominant form in the fetus and FMO3 the main form of the enzyme present in the adult human liver. Primary trimethylaminuria occurs as a result of mutation in the FMO3 gene, resulting in defective metabolism of TMA, and the first such mutation detected was that of P153L, although several mutations are now known to give rise to the primary form of the disease. Transient or mild forms of trimethylaminuria are recognized, and the development of trimethylaminuria in adulthood, without a medical history in childhood, is also recognized. Chronic hepatic disease, which leads to impaired metabolism of TMA, leads to an excessive amount of TMA in the urine with a resultant fishy malodor. Secondary trimethylaminuria has been described in a patient who was also found to have a homozygous G→A nucleotide substitution in exon 4, resulting in a glutamic acid to lysine substitution at residue 158.

Trimethylaminuria is suspected or declares itself when children are weaned and/or when a food that contains a TMA-precursor is introduced into their diet. Trimethylamine gives rise to an offensive odor in secretions, such as sweat, saliva, and vaginal secretions, and trimethylaminuria is recognized as an important systemic cause of halitosis. Although the human sense of smell can be very sensitive to the odor of TMA (the olfactory threshold is reported to be 0.00037 ppm), some individuals are less able to detect the odor of TMA.

The cardinal feature is self-declaration of the malodor or detection by friends or relatives. The odor may be enhanced following exertion, temperature rises, and emotional changes; may occur intermittently; and is known to increase in women just prior to and during menstruation as a result of hormonal inhibition of TMA oxidation. Trimethylaminuria has been reported in association with other clinical entities, such as the Prader-Willi syndrome, seizures, and behavioral disturbances.

Distressing psychosocial accompaniments of trimethylaminuria include withdrawn personality, social isolation, obsessive personal cleansing, depression, interrupted schooling, marital disharmony, and suicidal intent.

Some breeds of chicken, such as the Rhode Island Red, are known to produce eggs with TMA odor as a result of defective N-oxidation of TMA (Figure). Some breeds of chicken, such as the Rhode Island Red, are known to produce eggs with TMA odor as a result of defective N-oxidation of TMA. FMO3 deficiency is considered to be rare in children.

Most individuals within a British white population are known to be able to convert over 90% of their dietary-derived TMA to its N-oxide (TMNO). Ethnic variation in the ability to N-oxidize TMA is recognized. The hepatic enzyme TMA oxidase converts TMA to the nonodorous trimethyl oxide, which is then excreted in the urine. Trimethylamine and TMNO, although regarded as being nontoxic, are now considered to have the potential to form the carcinogen N-nitrosodimethylamine. The TMA N-oxidation is catalyzed by an FMO.

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combination of proton nuclear magnetic resonance spectroscopy and gene sequencing methods.34-37 Gas chromatography, isotope dilution, and solid-phase microextraction are other techniques that have been used to detect increased amounts of TMA in the urine of patients with suspected trimethylaminuria.38-40

Of prime importance is explanation of the condition to patients. Genetic counseling needs to be discussed in relation to primary trimethylaminuria. Antiperspirants, deodorants, and frequent bathing to rid the skin of the malodorous secretions are useful approaches.41 Soaps with a pH level of 5.5 to 6.5 have been reported to be useful in the reduction of body odor.42 A choline-controlled diet to reduce intake of choline-containing food (eg, eggs, peas, beans, marine fish, liver, and kidney) may be beneficial.43 In a study of several food items tested in individuals, increased urinary levels of TMA and the oxide occurred only following ingestion of fish and seafood.44 Milk elimination was found to be useful in a case in which ingestion of large quantities of milk was associated with excessive TMA excretion in urine.45 Brussels sprouts are known to be a rich source of the substance progoitrin, which reduces the TMA oxidation capacity in hens. It has been suggested that reduction of the intake of vegetables of the Brassica family may be of potential benefit for patients with trimethylaminuria.46 Antibiotic therapy may also benefit patients, particularly at times of stress, exercise, emotional upset, and menstruation or when dietary restriction is relaxed. Reduction of the intestinal bacterial load with lactulose, metronidazole, and neomycin sulfate can be helpful.47-49 In a study of 7 Japanese patients with trimethylaminuria, activated charcoal and copper chlorophyllin were found to reduce urinary free TMA and to increase the concentration of TMAO, thus having therapeutic potential in the treatment of patients.50

Suggested therapeutic strategies for the future include replacing deficient genes for FMO3 and attempting to colonize the human gut with microorganisms engineered with human FMO3.51 Flavin-containing monooxygenase 3 is also known to be involved in oxidative detoxification and metabolism of several substances and drugs; thus, its enzyme variability is considered to have metabolic and clinical implications beyond body malodor.52-56 Total parenteral nutrition has been found to have a detectable effect on modulation of rat FMO3, FMO4, and cytochrome P-450E1 (CYP2E1) monooxygenase activity, and it is postulated that these findings may have clinical relevance to patients receiving total parenteral nutrition and individuals with trimethylaminuria.57

The first international workshop on trimethylaminuria was held at the National Institutes of Health in Bethesda, Md, in 1999 to discuss and facilitate research into this rare entity. Support groups, such as the Trimethylaminuria Foundation (which can be contacted at trimth411@aol.com), provide information to patients about this rare syndrome.58

In conclusion, trimethylaminuria can occur in the primary genetic form or the secondary acquired form. A high index of suspicion should be maintained when treating patients who report real or perceived body malodor. Confirmation of the diagnosis and early institution of dietary and pharmacological measures are vital in the treatment of these patients. Genetic counseling needs to be considered in relation to the primary form of the syndrome. Providing patients with relevant information and introducing patients to support groups form an important aspect of the management strategy. Further research is likely to lead to novel concepts, which will add to therapeutic strategies available to clinicians who treat patients with this rare and distressing disorder that has a major impact on quality of life.

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