Review Article

Trimethylaminuria: Causes and Diagnosis of a Socially Distressing Condition

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Abstract

Trimethylaminuria is a disorder in which the volatile, fish-smelling compound, trimethylamine (TMA) accumulates and is excreted in the urine, but is also found in the sweat and breath of these patients. Because many patients have associated body odours or halitosis, trimethylaminuria sufferers can meet serious difficulties in a social context, leading to other problems such as isolation and depression. TMA is formed by bacteria in the mammalian gut from reduction of compounds such as trimethylamine-*N*-oxide (TMAO) and choline. Primary trimethylaminuria sufferers have an inherited enzyme deficiency where TMA is not efficiently converted to the non-odorous TMAO in the liver. Secondary causes of trimethylaminuria have been described, sometimes accompanied by genetic variations. Diagnosis of trimethylaminuria requires the measurement of TMA and TMAO in urine, which should be collected after a high substrate meal in milder or intermittent cases, most simply, a marine-fish meal. The symptoms of trimethylaminuria can be improved by changes in the diet to avoid precursors, in particular TMAO which is found in high concentrations in marine fish. Treatment with antibiotics to control bacteria in the gut, or activated charcoal to sequester TMA, may also be beneficial.

"What have we here? A man or a fish? Dead or alive? A fish; he smells like a fish; a very ancient and fish-like smell; a kind of not of the newest Poor John"

William Shakespeare, The Tempest II. ii.26-29.
(A 'Poor John' was a dried hake)

History

Individuals with a pungent body odour resembling the smell of dead fish have been remarked on since ancient times: perhaps that acute observer of the human personality, William Shakespeare, had met somebody with this condition, which in *The Tempest* he ascribed to the deformed and savage slave Caliban.

There are said to be two allusions to this condition recorded during the 19th century in *The Lancet*, which it has not proved possible to trace, but the first clear clinical case report is attributed to Humbert *et al.* in 1970.[1] Their patient, a six-year-old child, was under investigation for a presumably unrelated immunodeficiency disorder, but her mother also complained that she periodically had a marked fish-like smell. Humbert *et al.* documented that unmetabolised TMA in body secretions and urine was the offending agent.[1] They showed that the patient increased her urinary TMA by 67% after a 15 mg/kg oral dose of TMA, in contrast to excretion by three control patients. A subsequent liver biopsy on this patient confirmed abnormal enzyme kinetics as predicted.[2] There have been numerous contributions since, on clinical presentations, knowledge of the relevant biochemical system, and the mutation and population genetics of the disorder. Both primary genetic and acquired causes of the symptom have been described. Although the incidence of the disorder is not known, more than 200 cases have been described, and from previously being considered rare, the condition may now be said to be uncommon.

Clinical Presentation

Patients present, usually in childhood or early adulthood, complaining of the body odour and/or halitosis, and samples are referred to the laboratory by general practitioners, general and metabolic paediatricians, endocrinologists,

dermatologists and others. The occurrence of this complaint comes up readily on internet search engines by entering such words as 'body odour', and there are patient advocacy groups in some developed countries. Intriguingly, many individuals have learned by trial and error how best to manage the disorder, including avoiding marine fish in their diet, and frequent washing and changing of clothes, so that patients often have little body odour when they present. In other cases, the subject may not be aware themselves of the malodour, and many cases have been identified with no overt malodour at all.[3] Although it may appear to be of small medical concern, in fact sufferers regard it as having a major social impact, with consequences for self esteem, employment, social isolation impairing formation of relationships and mood disorders, and rare cases of attempted suicide have been recorded.[4-6]

Defect in Trimethylaminuria

In subjects with trimethylaminuria, there is a disparity between the quantity of TMA acquired from the diet requiring oxygenation, and the ability of the hepatic microsomal enzyme system to oxidise this load, such that excess TMA accumulates and is excreted in the urine, but also appears in the sweat and other bodily secretions, and can be detected in the exhaled breath. The critical enzyme is the hepatic microsomal flavin-containing monooxygenase FMO3, which has a Km for TMA variously reported as about 170–310 μmol/L,[2] 15.3 ± 5 μmol/L,[7] and 31 ± 3 μmol/L.[8] The differences appear to be due to variations in pH and other reaction conditions. Many mutations and non-pathogenic sequence variants have been described. Although the complaint originally came to attention because of the occurrence of rare individuals with a primary genetic deficiency of the enzyme, as is commonly the case, subjects with less severe secondary and mixed forms of the complaint have since been described.

Primary Trimethylaminuria

The primary genetic form of the disease comprise the majority of the reported cases, and clinical symptoms confirmed genetically as due to inactivating mutations and less severe polymorphisms in the *FMO3* gene reported from populations in the USA (including Caucasians, African Americans, Hispanics and Asians), Canada, UK, Spain, Italy, Korea, Japan, Australia (including a patient of Greek ethnicity), Norway and Thailand.[9-24] The disease is most likely therefore pan-ethnic. While fully inactivating mutations cause severe and persistent malodour, less severe mutations and apparently benign polymorphisms may reduce the substrate threshold for developing symptoms.[25,26]

Secondary (Acquired) Trimethylaminuria

Cases of trimethylaminuria have been described where there was no genetic predisposition, or at least less than fully inactivating mutations of the *FMO3* gene as described above, but where a combination of dietary, gut metabolism, hormonal and enzyme expression may have been factors.

Transient Childhood

A premature neonate and several older children have been described,[27,28] in the first case after being fed choline-containing formula. Some sequence variations of uncertain significance were noted, but it is possible that the low enzyme levels associated with childhood (see below) and more or less substrate overload were contributory factors.

Transient Menstrual

A single female was shown to develop trimethylaminuria immediately prior to the onset of menstruation, though it has been mentioned anecdotally.[5,29] In a recent study, TMA excretion each day for one month in six healthy females was compared with six males.[30] All six females show striking increases in TMA excretion in the perimenstrual period. A further study confirmed perimenstrual trimethylaminuria in Japanese women who were homozygous for inactivating mutations, carried common polymorphisms, or were homozygous wild type.[31] The steroid nuclear receptor does not bear a response element, so how these changes are mediated is not known.[3] This lead the authors to speculate that, since males have a lower threshold for olfactory perception of TMA, there may be a physiological survival role for perimenstrual TMA excretion, in that it may dissuade the male from seeking what the authors describe as 'sexual congress' with an infertile female.[30] Interestingly, about 7% of normal people have a specific anosmia for TMA.[32]

Viral

In three cases the condition seemed to appear in adult life following an episode of possible viral hepatitis.[33,34] Increased TMA excretion and reduced oxidising capacity have been detected in a Japanese cohort with increased liver enzymes.[35]

Dietary Precursor Overload

Cases of trimethylaminuria have occurred after therapeutic administration of choline 8–20 g/day for the treatment of Huntington's chorea and Alzheimer's disease.[36,37]

Gut Flora and Hepatic Disease

Both portosystemic shunting and severely impaired hepatocellular function have reported to cause trimethylaminuria in a few cases, thought to be due to decreased clearance of the absorbed TMA load, and failure of oxygenation.[38,39] Bacterial overgrowth in the small bowel may increase TMA production, and this may contribute to the odour associated with uraemia.[40,41] Given that even on the same dose of substrate precursor in loading tests there is a

big variation in the amount of TMAO and TMA excretion, it is possible that the nature of the gut microflora may play a significant role in the generation of symptoms in some individuals.[42]

Biochemistry

Trimethylamine

The structure of TMA is shown in Figure 1. It is a tertiary amine, very volatile at ambient temperatures and extremely readily detected by the human olfactory system, at levels of 0.12 ppb, with men more sensitive than women.[43] Marine fish contain large amounts of the *N*-oxide TMAO which plays a major role in osmoregulation, allowing marine fish to colonise a profoundly saline environment. Bacterial activity in rotting fish reduces the TMAO to TMA, imparting the characteristic odour, and the human ability to detect this odour so readily has led some to suppose that this may have a role in preventing humans from ingesting rotten fish.

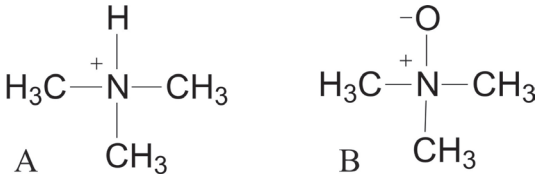

Figure 1. Structure of (A) trimethylamine (TMA) and (B) trimethylamine-N-oxide (TMAO). TMA is protonated at physiological pH.

In the human, dietary TMAO ingested in marine fish is reduced to TMA by the colonic microflora and absorbed by passive diffusion across the cell membranes.[44-46] It enters the enterohepatic circulation and is removed by the liver. In normal liver cells, TMA is oxygenated back to the odourless TMAO by the microsomal flavin-containing monooxygenase FMO3.[47,48] These steps are shown diagrammatically in Figure 2. TMAO so formed is very water soluble and in the normal subject is excreted mainly in the urine.

Choline is present in the diet both as choline and as a component of lecithin and originates from peas and beans, organ meats and egg yolks. The total daily free choline intake is about 9 mg, and the 2.1 g of choline which provoked an increased methylamine excretion were well in excess of this.[42] It is absorbed throughout the small intestine,[49] and excess choline transiting to the large bowel is metabolised to methylamines by colonic bacteria.[42] The absorbed fraction is either used directly, for example as a component in cell membranes, or is metabolised to glycine betaine in the

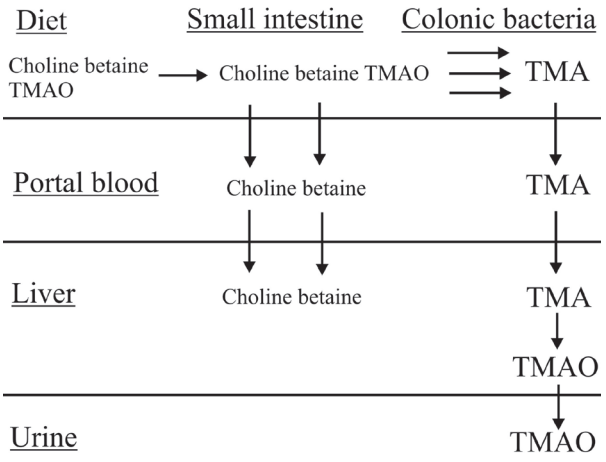

Figure 2. Interrelation of diet sources of precursor substances and normal TMAO metabolism. TMA = trimethylamine; TMAO = trimethylamine-*N*-oxide.

mammalian liver.[50] Choline is not converted directly to methylamines in human tissues; intraperitoneal injection of choline into rats does not provoke an increase in methylamine excretion.[51]

Lecithin or phosphotidylcholine is 13% choline by weight. However, even the large doses of 11.65 g lecithin used in the above study did not provoke an increase in urinary total methylamine excretion, so although it is still not clear if lecithin is hydrolysed in the jejunum, it would not appear to be a factor anyway. Colonic bacteria could generate methylamines from lecithin, but it must require very large oral intake.[52]

Carnitine is produced both naturally as the L isomer in human tissues and absorbed actively and passively from the diet.[53] It is excreted unchanged in the urine. Dietary L-carnitine in meat does not cause excretion of total methylamines.[42] It is used medically as a supplement in some fatty acid oxidation and organic acid disorders and can also be converted to TMA by colonic bacteria,[52] such that large doses are anecdotally known to provoke a fishy odour in some susceptible individuals.[54]

Glycine Betaine

There is no evidence that this is converted to TMA and the oxide in human tissues, and intraperitoneal injections of glycine betaine in rats does not provoke an increase in methylamine excretion.[50] However, colonic bacteria may convert glycine betaine to methylamines, and large doses given medically, as in homocystinuria, have anecdotally been known to provoke a fishy odour.[54]

The Biochemistry of the Flavin-Containing Monooxygenases

The flavin-containing monooxygenases are a family of enzymes which detoxify a broad spectrum of dietary xenobiotics, including natural plant alkaloids, and in modern humans, synthetic environmental toxicants. These enzymes have a role in metabolism of some drugs and possibly some endogenous amines.[55-57] The flavin-containing monooxygenases catalyse NADPH-dependant oxygenation of substrates which have nucleophilic N, S, Se, or P centres.[58] The members of this family have both individual and overlapping specificities, and expression of the enzymes is tissue, species, development and even in some cases gender specific.[59] Five translated members of this family with separate genes have been described in humans.[60]

FMO1 is expressed both at the mRNA and protein level in the human liver during the first trimester, but wanes gradually in the second and third trimesters, disappearing completely by about the third post natal day irrespective of gestation.[61,62] The cause of this disappearance is not known, nor is the precise role of this enzyme in the foetus known, though TMAO is not a substrate.[63] Small amounts of FMO1 mRNA are also found in the adult small intestine, but by far the most is in adult kidney.[62]

FMO2 is expressed in the lung of 26% of African Americans and 4.5% Hispanic people, and not at all in Caucasian or Asian persons.[3] Interestingly, FMO2 mRNA is found in all people but does not translate to mature protein, because most people have an inactivating truncating mutation and the mRNA is subject to nonsense-mediated mRNA decay.[62] FMO2 probably also has a detoxification function.

FMO3, both mRNA and protein, mutations of which cause trimethylaminuria, is first identified in 30% of foetal livers in the first trimester of pregnancy, disappears in the second and third trimesters, but identified again by 21 post-natal days irrespective of gestation. This gradually increases to 8% of adult levels at about nine months age, 20% by 11 years, and even by 18 years the level of FMO3 is still significantly below adult levels. There is therefore a remarkable switch of enzyme form from FMO1 in foetal liver, to FMO3 as well as FMO5 in adult liver. The causes of this switch are not known.[61,62]

FMO4 has proved more difficult to study because it is less easy to purify, and the protein is less stable, so the pharmacokinetic and substrate specificities are not clear, much less the role in metabolism.[64] However the mRNA is certainly significantly expressed in adult liver and kidney.[62]

FMO5 mRNA is present in the adult liver in similar amounts to FMO3,[62] and has significantly different substrate specificities.[59] It is the most significant mRNA in intestinal tissue, prompting the suggestion that it may have a role in intestinal first-pass metabolism, though others consider a physiological role, as opposed to a detoxification role also possible.[59]

Genetics of FMO3 and Variants

It is apparent that primary and secondary TMA may be interrelated, as hereditary, age, environmental, physiological and genetic factors may combine, where sequence variants decrease active FMO3 expression, to give rise to the disorder.

FMO3 Gene

The *FMO3* gene is a member of a family of flavin-containing monooxygenases which, in humans, has five forms (FMO1–5) and six pseudogenes (FMO6P–11P).[65] The FMO isoforms 1–4 and pseudogene FMO-6P are clustered on the long arm of chromosome 1 (q23-25) and the remaining genes are localised in a second cluster 4 Mb telomeric of the original cluster. The *FMO3* gene, located at 1q24.3, encodes the major metabolising isozyme in the adult human liver. The gene, encoding the 60 kDa protein, spans 27 kb and consists of nine exons, including exon 1 which is non-coding.[65]

FMO3 Variants

To date more than 300 variants or single nucleotide polymorphisms (SNPs) have been recorded in the gene,[66] including more than 40 variants that have been associated with trimethylaminuria. A number of these variants have been identified as pathogenic mutations that essentially abolish FMO3 activity causing primary trimethylaminuria and are therefore null mutations.[13,15,67,68] As trimethylaminuria is inherited in an autosomal recessive manner, heterozygotes or carriers of only one FMO3 mutation are asymptomatic. The incidence of carriers varies between ethnicities, ranging from 0.5–1% in white British populations to around 11% in New Guinea.[69]

The majority of pathogenic mutations described are missense mutations (reviewed in Hernandez *et al.*).[67] Nonsense mutations, small deletions (1 or 2 bp) resulting in frameshift mutations and one large deletion (12.2 kb) have also been reported. The first mutation to be identified in a trimethylaminuria patient is one of the two most common mutations identified to date, c.458C>T (p.Pro153Leu).[15] The other common mutation is nonsense mutation c.913G>T (p.Glu305X).[70]

In addition, a number of these variants do not lead to primary trimethylaminuria but contribute to a more transient or mild phenotype. For example, in a homozygous state or when c.472C>T (p.Glu158Lys) and c.23A>G (p.Glu308Gly) are on the same chromosome (in *cis*) there is a moderate

decrease in enzyme activity causing mild or transient trimethylaminuria, particularly in infants and young children who have low expression of FMO3.[22,26] The only SNP reported to result in an increase in enzyme activity is c.1079T>C (p.Leu360Pro).[71]

Mechanisms regulating *FMO3* transcription are of particular interest because of the temporal and tissue-specific nature of expression. In one study,[72] important transcriptional regulatory domains were identified within the promoter, containing NFY, USF1 and YY1 (among other) constitutive expression elements, plus Pbx_2/Hox and NF-E2 elements which may contribute to developmental and tissue-specific expression. In a later study of sequences further upstream, a C/EBPβ element was located.[73]

Investigation

In subjects with a history of malodour, urine can be readily analysed for TMA and TMAO. The results, expressed as μmol/mmol creatinine, can also be given as an 'oxidising ratio' TMAO/(TMAO + TMA) x 100%. Affected individuals with two inactivating mutations have a ratio of <84%[74] although when severely affected, most of the metabolic product is TMA. Unaffected individuals have a ratio >92%. However, it is essential that the oxidising capacity of the enzyme is sufficiently tested with substrate loading, otherwise a deficiency of the oxidising capacity may not be uncovered. Since many subjects have already discovered empirically what provokes the odour there is a significant chance that adequate substrate has already been excluded from their diet. This may cause difficulty particularly for the confirmation of the less severe forms of trimethylaminuria. There are no guidelines as to what constitutes adequate excretion of the total products, but we believe that a combined excretion of less than several hundred μmol/mmol creatinine could allow the diagnosis to be missed. It has been suggested that the threshold for the detection of symptoms is at a urine TMA concentration of 18–20 μmol/mmol creatinine.[75]

The most practical method of ensuring sufficient substrate is a 300 g marine fish meal followed by a random urine collection 2–12 hours after the meal or alternatively in the Nijmegen protocol, timed urine collection for 6–8 hours post meal.[74] Because the condition may be mild and/or intermittent, it may be necessary to test more than once, during times when the odour is prominent, before the diagnosis can be established.

Loading Tests

Because it is so important to ingest sufficient substrate to maximise flux through the oxidising system, several standardised methods of doing so have been used. Initially, choline was used.[76] Trimethylamine 600 mg orally was found to distinguish obligate carriers from normal and affected subjects,[77] whereas a dose of 300 mg failed to do so, and 900 mg was found to saturate the pathway. For reasons which are not known, some loading tests fail on occasion to provoke satisfactory excretion of metabolic products and this may be caused by factors such as the nature of gut colonisation, gut transit time, and delayed gastric emptying.

Genetic Confirmation

In subjects with severe and persistent symptoms and confirmed excretion of excess TMA even at low levels of substrate intake, it is arguable whether mutation analysis adds a great deal to diagnosis. However, there remain a number of patients with a suggestive history of mild or intermittent symptoms, in whom the nature of the genetic contribution to phenotype may improve understanding and treatment.

Other Metabolic Consequences of FMO3 Deficiency

Trimethylaminuria and Hypertension

There are theoretical reasons why decreased FMO3 function may affect blood pressure. For example, the enzyme may play a role in the inactivation of catecholamines.[78] In their review, Cashman *et al.*[3] refer to an unpublished study of 104 African Americans, in which they observed significant increase in the number of cases of uncontrolled hypertension in both males and females, relative to the number of cases in controlled and normal subjects. There was however no difference when the oxidation ratios themselves were compared. There are anecdotal reports of hypertension in patients.[22]

Trimethylaminuria and Affective Disorders

It is common for patients to experience mood disorder of variable severity and frequency, but it remains unclear whether this is owing to the socially isolating nature of the condition, or whether there is a biochemical component. For example, endogenous amines some of which are present in the brain such as tyramine are substrates for FMO3.[78]

FMO3 and Drug/Xenobiotic Metabolism

The substrate specificity of FMO3 is, like other mixed function oxidases, quite wide. As well as TMA and some plant alkaloids, FMO3 has activity against the medical drugs cimetidine, ranitidine, chlorpromazine, tamoxifen, sulindac, ketoconazole, propranolol and morphine,[74,79] as well as tyramine. The contribution made to net drug and xenobiotic metabolism is not known, but adverse reactions by trimethylaminuria subjects to tyramine and sulfur containing drugs have been mentioned, although most tyramine will be metabolised by monoamine oxidases.[22]

Analysis of Trimethylamine and Trimethylamine-*N*-oxide

Because TMA and TMAO have no native chromophore,

analysis requires the use of specialised instrumentation. Methods used for measuring urine TMA and TMAO include: proton nuclear magnetic resonance (^{1}H NMR) spectrometry,[80-82] headspace gas chromatography (GC),[83,84] electrospray ionisation tandem mass spectrometry (ESI-MS/MS),[85] direct infusion electrospray quadrupole time-of-flight mass spectrometry,[86] and matrix-assisted laser desorption/ionisation time of flight (MALDI-TOF) mass spectrometry.[87]

Advantages of using ^{1}H NMR to measure TMA and TMAO include the ability to measure both analytes from a single spectrum. Methylamines with multiple identical methyl groups generally give a large singlet in the proton spectrum, making quantification straight forward. TMA and TMAO have nine identical protons. Sample preparation for urine analysis by ^{1}H NMR is simple and involves diluting urine with 1 mol/L HCl containing an internal standard.[81] Deuterium oxide D_2O (lock standard) is also added either with the internal standard, or as a glass insert inside the NMR tube. Internal standards which have been used to measure methylamines by NMR include acetonitrile,[82] trimethylsilyl-2,2,3,3-tetradeuteropropionic acid (TSP),[80,81] and hexadeutero-4,4-dimethyl-4-silapentane-1 ammonium trifluoroacetate (DSA).[88] We have more recently found that trimethylacetonitrile (pivalonitrile) or trimethylacetamide (pivalamide) are convenient internal standards for the analysis of methylamines by ^{1}H NMR. These compounds contain three methyl groups like TMA and TMAO. Their resonances have a smaller chemical shift than acetonitrile and are in a region where there are fewer interfering peaks in biological samples. They are easier to handle and less volatile than acetonitrile, and in particular pivalamide is a water soluble non-volatile solid that can be conveniently weighed out. We have experienced inconsistent results using TSP as the internal standard, which are probably due to the low solubility of TSP in acidic solutions, especially when the ionic strength is high. DSA has been shown to be better than TSP as an internal standard, particularly for measuring metabolites in plasma and serum, because it does not bind to proteins.[88] However, DSA is expensive and has no advantages over pivalamide as an internal standard for NMR analysis of TMA and TMAO in urine. It is necessary to acidify urine samples for analysis by ^{1}H NMR, otherwise TMAO co-resonates with the methyl groups on glycine betaine.[50,81,89,90] Acidification of the samples separates the peaks so that TMAO is further downfield from the glycine betaine resonance. Previous reports have ignored the fact that TMAO and glycine betaine co-resonate at neutral pH, and have mistakenly quantified both glycine betaine and TMAO while only intending to measure one of them.[91] Acidifying the samples does however cause the TMA peak to split into a doublet, reducing the sensitivity. We have found that this can be avoided by adding aluminium chloride to the sample; the aluminium forms a complex with TMA and does not split the methyl proton resonance.

In order to quantify the data, external standards consisting of aqueous standards containing known concentrations of TMA and TMAO are measured on the same run. The peak area (or peak height) ratios of the analytes to the internal standard in the spectrum of the external standards are used to construct calibration curves. The peak area (or peak height) ratios to the internal standard are then used to quantify TMA and TMAO in the unknown samples. A water suppression technique can be used to remove the high water signal which swamps the NMR spectrum in aqueous solutions.

NMR spectrometers have a high capital cost, and are not currently available in most clinical laboratories, but are found in universities as a research tool. These research instruments are often not set up with autosamplers for quantifying batches of samples, and manually placing samples in the NMR spectrometer is time consuming. Other problems with NMR include relatively low sensitivity unless unacceptably long acquisition times are used, and often detection limits over 10 μmol/L[81] are tolerated as a practical compromise.

Measurement by GC requires TMAO to be reduced to TMA before analysis, and two separate injections are needed to measure the levels of both compounds in each sample.[83,84] The most common method of measuring trimethylamine by GC uses head-space analysis. The sample has to be made strongly alkaline to release unionised trimethylamine into the gas phase. However, reduction of TMAO to TMA is usually carried out in acid solution, using strong reducing agents such as Ti(III),[83,84] so there is a bulky precipitate when this is made alkaline. TMAO is quantified as the difference in the results between samples that have been treated with reducing agent and parallel ones not reduced. Nitrogen-phosphorus detection has been reported to be seven times more sensitive than flame ionisation detection for measuring TMA by GC.[92] GC-MS methods have also been described that derivatise TMA with reagents such as 2,2,2-trichloroethyl chloroformate.[84]

Liquid chromatography - mass spectrometry (LC-MS) is becoming increasingly popular in clinical settings. However, due to the small nature of the molecule, TMA is difficult to fragment using tandem mass spectrometry, and there are not many reports of LC-MS being used to measure TMA. Our attempts to measure trimethylamine using selected ion monitoring mode (LC-MS) have resulted in high detection limits. This was attributed to high background noise in the mobile phase due to the presence of compounds with a near-identical mass to TMA in common solvents such

as acetonitrile. However, tandem mass spectrometry with electrospray ionisation has been used to measure TMA and TMAO following derivatisation of trimethylamine with ethyl bromoacetate to form ethyl betaine bromide.[85] MALDI-TOF mass spectrometry has also been used to measure TMA and TMAO after derivatisation of TMA with iodomethane to form tetramethylammonium iodide.[86] Neither of these last two methods use a chromatographic component in the analysis. However, a more recent LC-MS/MS method has been described using ethyl bromoacetate to derivatise TMA, that separates TMA and TMAO on an HPLC column before detection by tandem mass spectrometry.[93] Given that LC-MS/MS systems are becoming increasingly more available in Australasian clinical laboratories, it is likely that tandem mass spectrometry will be used to measure TMA and TMAO in a greater number of laboratories in the future.

Treatment

To date there has been no systematic appraisal of suggested treatments in this condition, but it seems clear that the various options have not been universally successful,[94] particularly in severely affected individuals. At the very least, patients may benefit from being warned that the symptom may be exacerbated by febrile infections and during the perimenstrual period.

Hygiene

Frequent ablutions with a low pH soap (to minimise volatilisation from skin) and antiperspirants along with regular laundering of clothing seem sensible.[74]

Diet

Exclusion of the major source of TMAO from the diet, namely marine fish, is the primary dietary modality, and should not present a major difficulty. Choline is essential to the human and to some extent can be synthesised endogenously by methylation of phosphatidylethanolamine. But despite this endogenous production, a dietary deficiency may possibly lead to liver damage, neurological disease, and carcinogenesis.[95-99] Dietary reference intakes, based on observed and experimental estimates[100] and the content of various foods[101] have been published. A low substrate diet that requires minimising the intake of choline, lecithin and glycine betaine containing foods as well as marine fish is rigorous and potentially dangerous enough that professional dietary guidance and advice are necessary to prevent various dietary inadequacies. Requirements are higher in pregnant women, so restricting choline might be ill-advised. Given that only excess choline, lecithin and glycine betaine passing to the colon are metabolised to TMA by gut bacteria, it is far from clear whether ordinary dietary intakes would provoke symptoms. Since it appears that some vegetables, particularly Brussels sprouts, may inhibit hepatic FMO3 it is possible that further efficacy may be gained by limiting their intake.[102]

Antimicrobials

Brief courses of neomycin and metronidazole have been used to suppress gut microflora and are said to be useful in some but not all cases.[103] Although this may be useful in some milder and transient cases where gut colonisation is thought to be a factor, it would be unwise as anything more than a short term expedient.

Vitamin Supplementation

Restriction of choline intake may increase the requirement for folate.[104] Theoretically, since FMO3 has a flavin cofactor, riboflavin supplementation might augment the activity of the enzyme. There is no literature on the use of either vitamin in clinical practise.

Precursor Sequestering Agents

In one study, two self-reported patients with oxidising ratios below 90% were given oral activated charcoal, and a further three similar patients copper chlorophyllin, in order to bind precursor amines in the large bowel. All showed a suggestive reduction in TMA excretion and elevation of oxidising ratio.[105]

Summary

Trimethylaminuria is a disorder which may go for years undiagnosed, and is now known to be more common than was first thought. A patient's embarrassment about their body odour can often cause a reluctance to discuss the problem with their doctor. The condition exists in both severe primary genetic forms, as well as in less severe forms which are a mixture of genetic, constitutional and acquired factors. When testing a patient it is important to ensure that there has been sufficient intake of dietary precursors. The more widespread availability of equipment such as LC-MS/MS is giving more laboratories the ability to confirm a diagnosis of trimethylaminuria. While NMR methods are more efficient for measuring TMA and TMAO, this technology is not widely available in clinical laboratories in Australasia. Once diagnosed, the symptoms of trimethylaminuria can be improved by simple treatments, leading to a better quality of life for the patients.

Competing Interests: None declared.

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