

Trimethylaminuria

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Abstract

Trimethylaminuria, also known as "fish odor syndrome", refers to a rare inborn error of metabolism caused by impaired oxidization of the malodorous trimethylamine (TMA) into odorless trimethylamine N-oxide (TMAO). Trimethylaminuria is clinically characterized by a strong body odor of rotting fish resulting from abnormal excretion of trimethylamine in the breath, urine, sweat, saliva and vaginal secretions. TMA oxidation occurs in the liver and is mediated by members of the flavine monooxygenase (FMO) family. Human gene FMO3, whose product is the most abundant hepatic form, is highly polymorphic, and FMO3 mutations are associated with dysfunctional enzyme activity and expression of the metabolic syndrome. Proton NMR spectroscopy enables simultaneous measurement of urinary TMAO and TMA, and the determination of the ratio TMAO / (TMAO+TMA). The prevalence is estimated to be approximately 1 %, but is difficult to evaluate due to poor clinical awareness of the disorder. More cases are detected among women, probably as a result of their greater concern with the disease symptoms. Treatment consists essentially of dietary restriction (to reduce the intake of trimethylamine precursors, such as choline and carnitine), and short course of neomycin and metronidazole (400 mg/day). Drugs interfering with hepatic metabolism should also be avoided.

Keywords

trimethylaminuria, trimethylamine, trimethylamine-N-oxide (TMAO), dimethylglycine, fish-odor-syndrome, urine, proton NMR, flavine monooxygenase (FMO), choline, carnitine

Disease name and synonyms

- Trimethylaminuria
- Fish odor syndrome
- Fish malodor syndrome

Diagnosis criteria / definition

Trimethylaminuria, also known as "fish odor syndrome", refers to a rare inborn error of metabolism caused by impaired oxidization of the malodorous trimethylamine (TMA) into odorless trimethylamine N-oxide (TMAO), leading to the characteristic fishy smell. TMA oxidation occurs in the liver and is mediated by

members of the flavine monooxygenase (FMO) family.

Differential diagnosis

- i) Dimethylglycinuria, a malodor syndrome recently described, has been uncovered by proton NMR spectroscopy, a method also used for the detection of TMA and TMAO.
- ii) Other malodor syndromes.

Prevalence

The prevalence is estimated to be approximately 1%, but is difficult to evaluate due to poor clinical awareness of the disorder.

The number of detected patients increases with the greater medical awareness, and with the development of techniques, such as proton NMR spectroscopy, which enable fast and easy quantification of TMA and TMAO.

More cases are detected among women, probably as a result of their greater concern with the disease symptoms.

Clinical description

Trimethylaminuria is clinically characterized by a strong body odor of rotting fish resulting from abnormal excretion of trimethylamine in the breath, urine, sweat, saliva and vaginal secretions. The smell manifests in childhood, or later. Trimethylamine production can be intermittent and is exacerbated by puberty, sweating, menstruation, liver diseases, and mainly by a high dietary intake of sea fish, or meals rich in choline. In general, patients have no other trimethylaminuria-related health problems. Their problems are mainly psychosocial as they encounter difficulties in forming personal relationships at school, at work...

Management including treatment

- **Regimen:** the objective is to reduce the intake of TMA precursors, such as choline and carnitine. This dietary treatment is effective in mild to moderate forms.
- **Short course of neomycin and metronidazole** (400 mg/day), used to reduce the gut bacterial production of trimethylamine, can be effective in some cases.
- **Avoidance of drugs** interfering with hepatic metabolism.

Etiology

Inherited

Human gene *FMO3*, whose product is the most abundant hepatic form, is highly polymorphic, and some of *FMO3* mutations are associated with dysfunctional enzyme activity and expression of the metabolic syndrome. Other *FMO3* mutations appear, however, to be benign. Two common *FMO3* mutations, P153L and E305X appear to account for the majority of severe cases of fish odor syndrome.

Liver dysfunction

The following conditions, which alter liver enzymes metabolism, can reveal or increase trimethylaminuria especially in heterozygote subjects:

- viral hepatitis,
- toxic hepatitis,
- preterm infant whose liver enzymes, and the N-oxidase enzyme, are immature.

TMA precursor overload (especially in heterozygote form)

Aliments containing TMA precursors such as choline and carnitine, or large doses of choline (10 to 20 g/day) (used in diseases such as Huntington's chorea), can exceed the enzymes capacity to oxidize TMA (Growdan *et al.* 1977).

Menstruation

A transient urinary excretion of TMA may occur at the onset and during menstruation, even in the absence of any primary genetic cause.

Diagnostic methods

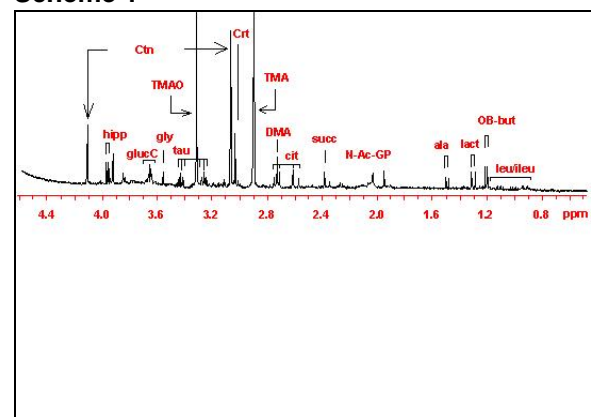
Diagnosis is based on the measurement of urinary TMA and TMAO before and after an oral load of 600 mg of TMA.

The classical biochemical method is based on the quantification of TMA excreted in urine by liquid chromatography. The amount of TMAO can be calculated indirectly as an increase in TMA, after its quantitative reduction by aqueous titanous sulfate.

When available, proton NMR spectroscopy is the preferential method of diagnosis. This technique enables the simultaneous determination of urinary TMAO and TMA, the calculation of the ratio $TMAO / (TMAO+TMA)$, and the measurement of dimethylglycine (DMG) for the differential diagnosis from dimethylglycinuria (see scheme 1). Proton NMR spectroscopy is a fast method which does not require any sample preparation, and enables the detection of any molecules whose concentration is higher than 10 μ molar.

The ratio $TMAO / (TMAO+TMA)$ is $96 \pm 2\%$ in unaffected patients following a normal diet. A drastic decrease in this ratio is observed in patients homozygote for trimethylaminuria. But an oral load of 600 mg of TMA is required to distinguish between ratios of unaffected patients ($95 \pm 2\%$) and heterozygote patients ($76 \pm 3\%$).

Scheme 1



Proton NMR spectroscopy of the urines obtained from a patient carrying an heterozygote form of trimethylaminuria, after an oral load of 600 mg of TMA. Reduction in the

ratioTMAO/(TMAO + TMA) which is 52 % is clear, whereas in a series of 5 controls, this ratio is $96 \pm 3\%$.

Abbreviations: trimethylamine (TMA), trimethylamine N-oxide (TMAO), dimethylamine (DMA), citrate (cit), succinate (succ), hippurate (hipp), glycine (gly), conjugated glucuronate (gluc-C), N acetyl glycoprotéines (N-Ac-Gp), taurine (tau), alanine (ala), leucine/isoleucine (leu/ileu), creatinine (Ctn), creatine (Crt).

Diagnosis at the molecular level shows that two common mutations of the *FMO3* gene, P153L and E305X appear to account for the majority of severe cases of fish odor syndrome

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