Tidsskriftet Tidsskrift for Den norske legeforening

Trimethylaminuria

SHORT CASE REPORT

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BACKGROUND

Trimethylaminuria is a rare disorder characterised by foul odour from bodily fluids and breath. The condition is caused by a homozygous mutation in the *FMO3* (flavin monooxygenase 3) gene coding for the enzyme that converts TMA *(*trimethylamine) to trimethylamine N-oxide. The result is elevated levels of secreted trimethylamine, which has a strong odour. The condition is likely to affect mental, emotional and social health. The diagnosis is reached by testing of free TMA (trimethylamine*)* and percentage N-oxidation in urine samples or by genetic testing.

CASE PRESENTATION

A man in his fifties had from childhood occasionally been told that his breath resembled rotten fish. He had searched for a diagnosis on the internet and was referred to testing for trimethylaminuria, and the diagnosis was confirmed.

INTERPRETATION

Urine test samples with high levels of free TMA and subnormal percentage of trimethylamine N-oxide revealed the diagnosis of trimethylaminuria. There is no causal treatment. Patients are advised to avoid choline-rich foods and take hygienic measures.

A man had been receiving comments about his unpleasant body odour for as long as he could remember. Assessment revealed a rare and underdiagnosed metabolic disorder associated with a severe psychosocial burden.

A man in his fifties sought medical advice after receiving multiple comments about his unpleasant body odour. He had been told from childhood that his breath smelt like rotting fish, especially a few days after consuming seafood. The patient searched the internet and began to suspect that he might have 'fish-odour syndrome'. He was referred to the endocrinology department for testing.

The doctor to whom he was referred could not say for certain that the man had abnormal body odour, but his history was typical of the condition, and assessment was therefore started. The man provided two 24-hour urine samples, which were acidified with hydrogen chloride to pH <2 and sent to Sheffield Children's Hospital. The urine samples showed reduced oxidation and markedly increased free trimethylamine (TMA) (Table 1). This confirmed the diagnosis of trimethylaminuria, also known as fish-odour syndrome.

Table 1

Analysis of the patient's 24-hour urine for diagnosis of trimethylaminuria. A high free trimethylamine (TMA)/creatinine ratio is seen when the flavin monooxygenase enzyme is defective. This also results in reduced oxidation of trimethylamine (N-oxidation).

	1st urine collection	2nd urine collection	Reference range
Free TMA/creatinine ratio	156.1	486	< 7.7 umol/mmol
N-oxidation	38	7	> 94 %
Urinary creatinine	19.3	9.79	mmol/L

Genetic tests were also performed, and revealed a well-known definitive pathogenic variant in the flavin monooxygenase 3 (*FMO3*) gene. Treatment for the condition consists of a specially adapted diet devised by a clinical nutritionist. Family and friends noted some improvement in symptoms after the change of diet; the challenge is that the patient himself does not notice his unpleasant body odour.

Discussion

Bad breath and unpleasant body odour are typical symptoms of trimethylaminuria, a condition that was first described in 1970 (1). The disease is caused by a homozygous mutation in the gene encoding the enzyme flavin monooxygenase 3 (*FMO3*) and shows autosomal recessive inheritance (2). The incidence of heterozygosity (carrier state) in the British population is 0.5–1 % (3). The disease prevalence is unknown, but is assumed to be up to 1 per 40 000 individuals (4). The condition is characterised by the odour of trimethylamine (TMA) in urine, sweat and exhaled breath. Trimethylamine is a tertiary amine with a characteristic odour reminiscent of rotting fish. The unpleasant odour can vary with food intake, the menstrual cycle, fever or stress (5).

In healthy individuals, choline and other trimethylamine precursors are degraded by the intestinal flora to trimethylamine, which enters the enterohepatic circulation where it is oxidised by flavin monooxygenase to the non-odorous trimethylamine N-oxide (TMAO). Patients with trimethylaminuria thus excrete foul-smelling trimethylamine in their bodily fluids as a result of insufficient oxidation (5).

The diagnosis is made biochemically by measuring the free trimethylamine/creatinine ratio and N-oxidation (TMAO / (TMA + TMAO) × 100) in 24-hour urine (6). This analysis is not currently performed in Norway. For the diagnosis to be confirmed, high free trimethylamine levels must be detected in two 24-hour urine samples. The individual being tested is advised to consume foods with a high choline content the day before urine collection (at least two meals with two eggs and 400 g of beans in tomato sauce), also referred to as trimethylamine loading. A urinary tract infection must be ruled out as this may also give rise to temporarily elevated trimethylamine levels in urine.

Patients with confirmed disease excrete 80 % of total trimethylamine (TMA + TMAO) as foul-smelling trimethylamine (TMA). Carriers excrete approximately 4 % as trimethylamine. Trimethylamine loading prior to urinalysis increases the excretion of trimethylamine by up to 25 % in heterozygous patients (5).

The diagnosis can be made either on the basis of a confirmed increase in excretion of free trimethylamine in urine or a positive genetic test, with either one being sufficient. Genetic testing is therefore not required to make the diagnosis, but genetic counselling is recommended in cases of confirmed disease.

Cases of secondary trimethylaminuria have been described in the literature, for example in patients who have received experimental treatment with high-dose choline for Huntington's chorea or Alzheimer's disease. Other rare causes of the condition include liver disease and chronic kidney failure (6).

Fish-odour syndrome is harmless as it does not give rise to organ damage. There is no established treatment for the enzyme deficiency. A number of drugs such as probiotics and laxatives have been tested, without any definite effect being confirmed. Activated charcoal at a dose of 750 mg × 2 orally for 10 days has been reported to reduce free trimethylamine in urine, as has copper chlorophyllin when administered over a longer period (5).

The best treatment is a diet containing only 200–300 mg of choline per day (7), compared to the recommended daily choline intake of at least 400 mg/day for the population as a whole (8). A low intake of foods containing choline and lecithin (precursors to trimethylamine) as well as indoles is recommended. This implies a low protein intake and in particular an increased intake of carbohydrates, possibly alongside increased fat intake to meet calorie requirements. In practice, patients must avoid foods such as saltwater fish and seafood, egg yolks (including dishes containing eggs and mayonnaise) and offal (kidneys and liver, including liver paté). Patients should also avoid eating brussels sprouts, broccoli, cauliflower, beans and products made with beans, especially soya beans.

The problem with a choline-poor diet is that choline deficiency is associated with a number of serious conditions including liver damage, neurological diseases and an increased incidence of malignancy (5).

Frequent washing with low-pH soaps is recommended along with the use of deodorant. Patients should also wash and change their clothes frequently. Patients should be informed that fever, stress, physical activity or hyperventilation may worsen their body odour. The psychosocial burden of trimethylaminuria can be considerable, with those affected experiencing an increased incidence of loneliness, social isolation, anxiety and depression (6). It is therefore important to diagnose the condition and to offer patients dietary advice and psychological support.

The patient has consented to the publication of this article. The article has been peer-reviewed.

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Publisert: 15 September 2021. Tidsskr Nor Legeforen. DOI: 10.4045/tidsskr.21.0142
Received 22.2.2021, first revision submitted 14.3.2021, accepted 30.5.2021.