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Classic diseases revisited

Fish odour syndrome

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Summary
Fish odour syndrome (trimethylaminuria) is a metabolic syndrome caused by abnormal excretion of trimethylamine in the breath, urine, sweat, saliva and vaginal secretions. Trimethylamine is derived from the intestinal bacterial degradation of foods rich in choline and carnitine and is normally oxidised by the liver to odourless trimethylamine N-oxide which is then excreted in the urine. Impaired oxidation of trimethylamine is thought to be the cause of the fish odour syndrome and is responsible for the smell of rotting fish. Certain foods rich in choline exacerbate the condition and the patients have a variety of psychological problems. Recognition of the condition is important as dietary adjustments reduce the excretion of trimethylamine and may reduce the odour. Occasionally, a short course of metronidazole, neomycin and lactulose may suppress production of trimethylamine by reducing the activity of gut microflora.

Keywords: fish odour syndrome; trimethylaminuria

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Humbert and colleagues[1] first described fish odour syndrome (trimethylaminuria) in 1970 in a 6-year-old girl who had the clinical stigmata of Noonan's syndrome (short stature, hypertelorism, ptosis, pulmonary stenosis, skeletal abnormalities and mental retardation) and splenomegaly, with intermittent body odour characteristic of rotting fish. Since then, other cases have been described, showing that trimethylaminuria is not necessarily associated with Noonan's syndrome, as observed in the initial case. It is caused by abnormal excretion of a tertiary aliphatic amine (trimethylamine) in the breath, urine, sweat, saliva and vaginal secretions.[2] This amine smells of rotting fish, and is readily detected by human nose at very low concentrations (<1 ppm).[3] Trimethylamine has a 100-fold greater olfactory potency than the oxide.

Trimethylaminuria was thought to be a rare condition, but evidence suggests that its prevalence is much higher than initially thought. In a study involving 82 Jordanian subjects, eight subjects (9.7%) excreted less than 80% of their total trimethylamine as trimethylamine oxide.[4] A similar study showed 1.7% of the Jordanian population, 3.8% of the Ecuadorian population and 11% of the New Guinean population excreted less than 80% of their total trimethylamine as the N-oxide.[5] In another study involving 421 British white volunteers, 16 subjects (3.8%) excreted less than 90% of their total trimethylamine output as N-oxide, of which six subjects (1.4%) excreted less than 80% as N-oxide.[6]

Trimethylamine is derived from the intestinal bacterial degradation of foods rich in choline and carnitine, such as egg yolk, liver, kidney, soybeans, peas and salt-water fish.[7] It is readily absorbed from the gut, and is normally oxidised by the liver to odourless trimethylamine N-oxide, which is then excreted in the urine.[8] In the fish odour syndrome, the oxidation of trimethylamine is impaired; this is thought to be due to deficient trimethylamine oxidase in the liver.

The syndrome appears to be inherited in an autosomal recessive fashion[2] and the incidence of heterozygous carriers of the allele for impaired N-oxidation is estimated to be of the order of 1%.[9] Normal individuals excrete about 1 mg of trimethylamine and 50 mg of trimethylamine oxide in the urine in 24 hours, but excretion varies with diet. N-Oxide enzymatic oxidation capacity is rarely exceeded on an average diet. However, normal individuals can smell of rotting fish if 20 g of pure choline is given to them orally.[10] This is because of the resultant excessive production of trimethylamine, which exceeds the capacity of the normal healthy liver to oxidise it to a non-odorous oxide.

Trimethylamine metabolism may also be impaired in patients with chronic liver disease.[11] A case of congenital intrahepatic portal–systemic shunt associated with trimethylaminuria has been reported.[12] The abnormal overgrowth of small intestinal bacteria in uraemic patients greatly increases trimethylamine liberation from the precursors in the diet and in association with reduced renal clearance, the trimethylamine levels increase in the circulation, to escape via the breath and sweat.[13 14] It has also been reported in association with temporal lobe epilepsy and behavioural disturbances, with response to a choline-restricted diet.[15] The vaginal discharge of women with bacterial vaginosis often has a prominent fishy odour and there is evidence that trimethylamine is the primary cause of this.[16]

Patients with this condition usually present in childhood, although it may be noticed in infancy or adulthood. It may be intermittent. Puberty, sweating, exercise, emotional upsets, menstruation, oral contraceptives, and foods rich in choline have been recognised as exacerbating factors. Goitrin, a compound present in a wide variety of brassica crops, inhibits the flavoprotein-containing monooxygenase system and has been shown to retard the N-oxidation of trimethylamine in chickens,[17] but not in humans.[18]

Patients have various psychosocial problems, but no physical abnormality. They may have strong feelings of shame, embarrassment, low self-esteem, social isolation, and anxiety and depression.[2] They may be unable to form or maintain relationships with the opposite sex and may turn to drugs and alcohol. Some patients exhibit an obsessive ritual of personal cleansing. These difficulties usually start at school, where they are ridiculed.

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Differential diagnosis of fish odour syndrome

- poor hygiene
- gingivitis
- urinary infection
- infected vaginal discharge
- advanced liver disease
- advanced renal disease
- rare inherited metabolic disorders

Box 1

Exacerbating factors in fish odour syndrome

- menstruation
- puberty
- pyrexial states
- stress
- a choline-rich diet: milk, sea fish, peas, soybeans, liver, kidney and egg yolk

Box 2

Fish odour syndrome should be differentiated from poor hygiene, gingivitis, urinary infections, infected vaginal discharge, and advanced liver and renal disease. Diagnosis is established by the demonstration of increased free trimethylamine in the urine, with reduced trimethylamine N-oxide. This cannot be done on thin-layer chromatography, but requires gas chromatography. Urine samples should be collected under aseptic techniques, acidified to pH 2.0 with hydrochloric acid, and kept frozen until assay to prevent the bacterial degradation of trimethylamine, which occurs normally in untreated urine.[19] The urine should be collected at a time when the odour is maximal, and while the patient is on a normal diet but without fish for 48 hours.

A trimethylamine loading test, using a dose of 600 mg of trimethylamine base and analysing the following 0–8 h urine collection, can be used to detect asymptomatic carriers.[20 21]

Treatment involves counselling and dietary adjustments. An explanation of the biochemical nature of the disorder and the exacerbating factors such as menstruation will relieve patients' anxieties greatly. Dietary adjustments include avoidance of choline-rich produce (eggs, liver, peas, soybeans and sea fish), which reduces the excretion of trimethylamine and may reduce the odour. The restriction of milk has proved useful in some cases.[22] Occasionally, a short course of metronidazole, neomycin[2] and lactulose[23] can suppress production of trimethylamine by reducing the activity of gut microflora. Soaps with a pH value 5.5–6.5 have been reported to reduce the odour dramatically in some patients.[24] They act by retaining secreted trimethylamine (a strong base) in a less volatile salt form. Gene therapy and enzyme induction with drugs provide hope in the future.

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