CASE REPORT

Trimethylaminuria

Numaera Sabir,¹ Elizabeth A Jones,² Beena Padmakumar³¹Department of Paediatrics, Pennine Acute Trusts, Oldham, UK²Manchester Centre for Genomic Medicine, Central Manchester Foundation Trusts, Manchester, UK³Department of Paediatrics, Royal Oldham Hospital, Manchester, UK

Correspondence to

Dr Numaera Sabir, numaera.sabir@doctors.org.uk

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SUMMARY

We report the case of a 9-year-old boy referred to secondary care with an unusual presentation of a fishy odour to his hands, feet, saliva and urine. Laboratory investigations including urine analysis and genetic testing confirmed the diagnosis of trimethylaminuria. The patient was referred to a geneticist and dietician, and consequently treated with dietary modification. He now has an arguably much improved quality of life.

BACKGROUND

Trimethylaminuria is a metabolic condition that causes the bodily odour of its sufferers to have a distinctive smell, likened to that of rotten fish. Inherited in an autosomal recessive manner, it has an incidence of up to 1% in the UK.¹ Despite this, the condition is rarely known among paediatricians. We therefore felt it important to present the case to raise awareness among paediatric trainees in the hope to improve diagnosing the condition, and consequently improving the quality of life of sufferers.

CASE PRESENTATION

The patient was the first child born to Asian second-degree consanguineous parents. He was born at term by normal vaginal delivery and reached all developmental milestones. There was no significant medical history. He had one younger sibling who was asymptomatic; however, his first cousin was reported to exhibit similar symptoms.

Initial presentation of the problem was fishy smelling urine. This was, in the primary care setting, suspected to be due to urinary tract infections, although urine cultures remained negative. The long-standing nature of the persistent fishy odour, which also affected his hands, feet and breath intermittently for the next 3 years, prompted his mother to seek medical advice, leading to a referral to secondary care.

On presentation, clinical examination was unremarkable. Following literature review, we made a provisional diagnosis of possible trimethylaminuria. The patient's urine was sent to exclude this diagnosis before any further investigations were performed. As the urine test came back positive, the diagnosis was then confirmed by DNA analysis.

INVESTIGATIONS

High levels of excreted trimethylamine (TMA) and a high TMA to TMA-N-oxide ratio were found in the patient's urine (as shown below). These changes coincide with those found in patients suffering from trimethylaminuria.

- ▶ TMA: 48.7 µmol/mmol creatinine—normal range (2.5–10.9)

- ▶ TMA-N-oxide: 70.0 µmol/mmol of creatinine—normal range (17–147)
- ▶ TMA/TMA-N-oxide ratio: 0.70—normal range (0.05–0.21)

Genetic testing confirmed that the patient was homozygous for the p.Glu208X,c.622G>T mutation in exon 5 of the flavin-containing monooxygenase 3 (FMO3) gene, confirming the diagnosis of trimethylaminuria.

DIFFERENTIAL DIAGNOSIS

Owing to offensive smelling bodily secretions, a number of differential diagnoses can be made. A common misdiagnosis of the condition is a urinary tract infection, as offensive smelling urine is often the initial presentation. Phenylketonuria, isovaleric acidemia, glutaric acidemia type II and maple syrup urine disease are all differential diagnoses, as each condition has a characteristic malodour to the urine of the affected individual.²

TREATMENT

The patient was managed conservatively, adapting a multidisciplinary approach between the paediatricians, geneticists and dieticians. The dietician gave advice to avoid foods containing TMA, choline, lecithin or TMA N-oxide; these include egg, liver, kidney, peas, beans, peanuts, soya products, brassicas and seafood. Dietary management helped to minimise the fishy odour.

OUTCOME AND FOLLOW-UP

The geneticist counselled the family and informed them about the autosomal recessive inheritance of the condition. The patient was then discharged from secondary care with advice to carry on the dietary plan.

DISCUSSION

Trimethylaminuria, also known as fish odour syndrome, is an autosomal recessive inherited disorder characterised by a body odour likened to rotten fish. This is a relatively rare disorder but the incidence of heterozygous carriers in the white British population has been suggested to be as high as 1.0%.^{1,3}

The condition is caused by deficient oxidation of the enzyme and consequent increased excretion of the unoxidised TMA, which gives rise to the characteristic fish odour smell. Factors including genetic predisposition, hormonal influences on expression and substrate overload, all influence the expression of the condition.

The different forms of trimethylaminuria are further discussed in this paper.

The primary genetic form accounts for a large proportion of the disease. TMA is derived from

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dietary precursors, such as choline and lecithin via the action of bacteria in the gut.^{4 5} It is metabolised in the liver by the FMO3 enzyme, to produce the non-odorous TMA N-oxide.⁶ Homozygous or compound heterozygous loss of function mutations in the FMO3 gene result in an excess of the odorous TMA. This is due to both the bodies' inability to catalyse the N-oxygenation of TMA, and the resultant large amount of substrate present. Consequently, affected individuals have a distinctive fish odour to all bodily secretions.⁷ Advances in the availability of genetic testing of the FMO3 gene have enabled genetic confirmation of the biochemical diagnosis.⁸

Case reports reviewed show rare cases of acquired trimethylaminuria that emerged in adult life. In these cases, there was neither familial nor personal history of the disorder, although common to all cases was the presence of previous or current liver pathology, such as hepatitis. It was therefore suggested that the acquisition of the disorder in these cases may be linked to insertion of viral DNA into the genome, which adversely affects the normal expression of the FMO3 gene.^{8 9}

Transient childhood trimethylaminuria is likely to be the consequence of immaturity of N-oxidase enzyme, which is turned on at birth and matures throughout childhood.¹⁰ Transient trimethylaminuria has been reported in preterm infants fed a choline containing diet. Symptoms resolved when the formula was changed, and did not reappear when choline containing foods were reintroduced.¹¹ Further cases due to compound heterozygosity of the defective FMO3 gene have also been described.^{8 12–14}

Transient trimethylaminuria has also been reported in women during menstruation, which suggests possible hormone modulation of FMO3.^{8 15} This was more pronounced in women homozygous for polymorphic variants that resulted in reduced FMO3 enzyme activity.⁴

Trimethylaminuria is also caused by precursor overload. This form results from saturation of the FMO3 enzyme. It can occur in individuals who have been given large oral therapeutic doses of trimethylaminuria precursors.

Although a difficult diagnosis to initially suggest, when reviewing the literature, a clear theme of malodorous bodily secretions is evident. Mayatepek *et al* studied two infants with transient trimethylaminuria in childhood. Both presented with offensive fishy smelling skin and urine. Equally, both had normal initial routine physical and biochemical parameters before urine was tested for TMA, after which its N-oxide and the diagnosis became highly likely.¹²

Two further case reports identified patients who both had distinctly malodorous bodily secretions as their initial symptom. Again, routine investigations were unremarkable, and specific urine and DNA analysis confirmed the diagnosis; in both cases a low choline diet improved symptoms.^{16 17}

Diagnosis of trimethylaminuria is a combination of clinical, biochemical and genetic tests. Urine can be tested for free TMA alone, or in combination with its N-oxide metabolite. Samples from affected individuals show abnormally high levels of the odorous free TMA or a high ratio of TMA to its N-oxide.⁴ With the advent of molecular genotyping and recognition of the causative FMO3 gene mutation and its many polymorphs, the primary genetic type can be readily identified.⁸

The mainstay of treatment for the disorder is dietary restrictions, targeting food groups containing high levels of both TMA, including its precursors such as carnitine and choline, and TMA N-oxide. In particular, foods such as eggs, liver, beans, brassicas and seafood should be avoided.^{7 8}

Other treatments have also been adopted and may be beneficial. Antibiotics such as metronidazole, neomycin and

amoxicillin can be used in short courses to suppress gut bacteria, consequently reducing the production TMA.¹⁸ The use of gut absorbents such as charcoal to sequester TMA production may also play a role. Furthermore, the use of soaps, lotions and fragrances can temporarily mask the odour in this condition.

Families may also gain significant benefit from genetic services. Educating individuals on the condition through dietary advice, as well as by addressing exacerbating factors including stress and menstruation, can also be beneficial.⁸

Learning points

- ▶ Individuals affected by trimethylaminuria have a strong fishy odour to their sweat, urine, breath and other bodily secretions.
- ▶ The odour can interfere with many aspects of daily life, affecting a person's relationships, social life and career. Furthermore, individuals with trimethylaminuria can experience depression and social isolation as a result of this condition, and so identification of this rare condition is very important.
- ▶ Early diagnosis and management by healthcare professionals can help patients and families deal with the condition. This is vital to improve the quality of life for sufferers and their families, and so a multidisciplinary approach to care must be organised and maintained.

Competing interests None declared.

Patient consent Obtained.

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