Inborn errors of amino acid metabolism are rare, but may present in outpatient endocrinology clinics. We report one such case, to raise awareness of the diagnosis and treatment of this uncommon and distressing metabolic condition.

A 25 year old caucasian female, was referred to our unit having complained to her GP of a fishy body odour. She was unable to detect this herself, but had been aware of people making indirect references to a smell of fish since the age of 7 years and had experienced significant distress and anxiety as a result. She did not notice any change with her menstrual cycle, or diet. She attempted to conceal the odour with repeated bathing, anti-perspirants, perfume and smoking. She had consulted a number of doctors since her early twenties and had tested negative for bacterial vaginosis. Her medical history included ocular migraines. She was taking the combined oral contraceptive pill and waterfall D mannose herbal supplement for recurrent cystitis. Physical examination was unremarkable and no body odour was apparent. The diagnosis of trimethylaminuria (TMAU) was suspected by her GP and confirmed by urinalysis, which revealed significantly elevated trimethylamine excretion 43.1 µmol/mmol of creatinine (reference range 2.5-10.9 µmol/mmol) and TMA/TMA-oxide ratio 0.35 (reference range 0.05-0.21).

Trimethylaminuria is an uncommon metabolic condition characterised by elevated levels of the volatile tertiary amine trimethylamine (TMA) in urine, sweat, breath, saliva and vaginal secretions resulting in an odour of rotting fish. TMA is generated from gut bacteria breakdown of the dietary precursors choline and carnitine, present in high concentrations in fish, eggs and pulses. Under normal circumstances hepatic N-oxidation of TMA by the flavin monoxygenase 3 enzyme (FMO3) results in trimethylamine-oxide, an odourless compound which is excreted in the urine. Elevated levels of TMA result from impaired enzymatic function, or precursor overload.

Primary trimethylaminuria is an autosomal recessive condition resulting from disabling mutations of both FMO3 alleles. Our patient underwent genetic analysis which showed mutations of both alleles of the FMO3 gene with a p.Arg492Trp mutation on one allele, which has previously been reported in patients with primary trimethylaminuria and a novel p.Arg223Gln mutation on the other allele, which is predicted to be pathogenic.

The incidence of primary TMAU is unknown, however in two studies the incidence of heterozygosity in a normal population was around 1%. It is likely that many cases are not identified due to failure of affected individuals to seek medical attention and failure of physicians to recognise the disorder. There appears to be a higher incidence in females, the cause of which is unclear. FMO3 mutations account for most cases of TMAU, however acquired and transient forms have been reported following viral hepatitis and in preterm infants given choline-containing dietary supplements. TMA levels are elevated in healthy women in the few days prior to and during menstruation and therefore timing of urinalysis is important when screening females. Transient TMAU has been identified when normal individuals are exposed to a significant precursor load, as was seen when large doses of choline were used therapeutically to treat patients with Huntington’s Chorea.
Although considered a benign condition, TMAU is associated with significant psychological sequelae including social isolation, anxiety and low self esteem. Treatment options are limited and a multi-disciplinary approach is preferable. Dietary modification to reduce the intake of choline and carnitine is effective in around 25% of individuals. Short courses of the antibiotics metronidazole and neomycin reduce gut flora and generation of TMA. Copper chlorophyllin and activated charcoal reduce absorption of TMA. Our patient has been referred to a metabolic centre with access to specialist physicians, dieticians and clinical psychologists. Since commencing the above treatments no-one has commented on her body odour and having a formal diagnosis has enabled her to discuss her condition for the first time with family and friends.