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CASE REPORT

Trimethylaminuria (fish malodour syndrome) in chronic renal failure

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Abstract
Trimethylaminuria (fish malodour syndrome) is a rare genetic metabolic disorder presented with a body odour which smells like a decaying fish. This odour is highly objectionable, that can be destructive for the social, and work life of the patient. Trimethylamine is derived from the intestinal bacterial degradation of foods that are rich of choline and carnitine. Trimethylamine is normally oxidised by the liver to odourless trimethylamine N-oxide which is excreted in the urine, so, uremia may worsen the condition. Uremia itself may cause more or less unpleasant odour. Poor uremic control may worsen the odour. We reported this case because Trimethylaminuria is not usually considered in the differential diagnosis of malodour in chronic renal failure and it is the first case that shown the association with Trimethylaminuria and chronic renal failure in the literature. Hippokratia. 2012; 16 (1): 83-85

Key words: chronic renal failure, fish malodour syndrome, trimethylamine N-oxide,

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Case

A Twenty-three-years old male with chronic renal failure who suffered from an unpleasant body odour was admitted to nephrology clinic.

Past history: Unpleasent odour was noticed before having preemptive living related renal transplantation. After the transplation the odour had became tolerable. He was treated for seven years on immunosupresives of steroids, azathioprine and cyclosporine; in last two years on steroids, mycophenolate mofetil and everolimus. The last year as the renal impairment occurred he started hemodialysis (HD) program. During HD treatment per oral L-carnitene was added to the treatment for muscle cramps. After L-carnitine treatment the odour became more objectionable and he lost the social life and also his work. We excluded poor hygiene, chronic genital infections, liver disease and uremia for the differential diagnosis of malodour and the preliminary diagnose was trimethylaminuria (fish malodour syndrome).

Diagnosis of trimethylaminuria is based on either the percent of total trimethylamine (free trimethylamine (TMA) plus the non-odourous metabolite TMA N-oxide) excreted in the urine as unmetabolized free TMA. This patient was anuric so these tests could not be performed. FMO3 is the only gene known to be associated with trimethylaminuria. Sequence analysis is available clinically was performed and diagnosed the disease (Figure 1, 2). L-Carnitene treatment has been stopped and the patient was referred to a dietitian for advice on foods that contain low amounts of choline and lecithin. Symptoms decreased significantly after he started home dialysis program.

Discussion

Historically, anecdotal descriptions of individuals with the fish malodour syndrome have been recorded across various millennia and cultures[1]. From Indian epic of the Bharata Dynasty[2] to William Shakespeare. John Arbuthnot (1667–1735), a mathematician and physician, wrote in his treatise on nutrition and foods, "The oils with which fishes abound often turn rancid, and lie heavy on the stomach, and affect the very sweat with a rancid smell, which is found to be true in some places, where the inhabitants live entirely upon fish"[3]. The first clinical description of a case of fish malodour syndrome is attributed in 1970. The patient was a 6-year old girl with a

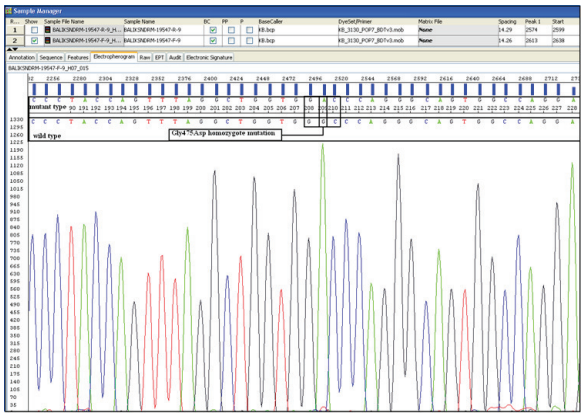

Figure 1: Genetic sequence analysis.

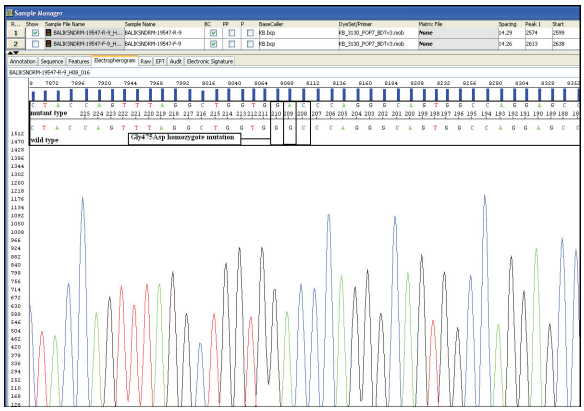

Figure 2: Genetic sequence analysis.

history of multiple pulmonary infections since the neonatal period. The child had the clinical stigmata of Turner's syndrome, a search for trimethylamine, which was known to smell of fish. Biochemical studies following an oral challenge dose of trimethylamine showed that there was a marked increase in the excretion of the free amine in her urine as well as a pronounced exacerbation of her odour problem. Three healthy controls did not show these increases[4]. A population and pedigree study confirmed that the *N*-oxidation of trimethylamine in a White Caucasian population was under genetic control and displayed polymorphism[5]. This study of a random British white population group showed that the ability to *N*-oxidize trimethylamine derived from the diet was skewed in terms of the population distribution. Based upon a metabolic ratio of urinary trimethylamine/trimethylamine *N*-oxide, metabolic "outliers" could be discerned. Patients diagnosed with fish malodour syndrome occupied one extreme of the distribution, and pedigree studies involving the use of an oral trimethylamine challenge test[5] revealed that the parents could be identified as carriers or heterozygote for dysfunctional *N*-oxidation.

Fish malodour syndrome should be differentiated from poor hygiene, gingivitis, urinary infections, infected vaginal discharge, and advanced liver and renal disease. In uremia simple nitrogen-containing solutes that accumulate include the aliphatic amines monomethylamine, dimethylamine, and trimethylamine. These compounds are produced by both gut bacteria and mammalian cells. They are positively charged at physiologic pH, and their removal during intermittent hemodialysis may be limited by their preferential distribution within the relatively acidic intracellular compartment[6]. The uremic fetor, or fishy breath, of patients with uremia is attributable to trimethylamine, and amines have been associated with impaired brain function in both patients and animal models[7-9].

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[10]. 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 two days.

Treatment involves counseling 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[11]. Occasionally, a short course of metronidazole, neomycin[12] and lactulose[13] 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[14]. They act by retaining secreted trimethylamine (a strong base) in a less volatile salt form. Since the human FMO3 participates in the oxygenation of nucleophilic heteroatom-containing drugs, xenobiotics, and endogenous materials, for treatment of deficiency gene therapy and enzyme induction with drugs provide hope in the future.

Biochemical testing of sibs to identify those who are affected and will benefit from management to reduce production of trimethylamine. Trimethylaminuria is inherited in an autosomal recessive manner. Prenatal testing may be available through laboratories offering custom prenatal testing for families in which the disease-causing mutations have been identified.

Conclusion

The incidences of the fish malodour syndrome not clear because new cases are continually being recognized and greater awareness of this metabolic problem. It is uncommon disorder it would seem that well over 200 cases of the condition have been described on a world-wide basis, and this figure is almost certainly underestimated especially among chronic renal failure patients. The condition has been observed in both males and females, although overall there appears to have been a preponderance of females reported with this condition[1]. This was the first report of Trimethylaminuria (fish malodour syn-

drome) in chronic renal failure and we expect the more uremic patiens will be diagnosed as Trimethylaminuria.

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