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Trimethylaminuria: A Rare Metabolic Disease Case Report

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ABSTRACT

Background: *Trimethylaminuria (TMUA) is a rare metabolic genetic disorder caused by a deficiency of flavin-containing monooxygenase 3 (FMO3). The disorder is clinically characterized by a distinctive odor known as fish-odor syndrome. Trimethylaminuria follows an autosomal recessive inheritance pattern. It is caused by homozygous or compound heterozygous mutations in the flavin-containing dimethylaniline monooxygenase 3 (FMO3) gene, located on chromosome 1q24. Here, we present the case of a girl who suffers from an unpleasant odor, which has an embarrassing effect on her social activities.*

Materials and Methods: *We report a female child of Saudi origin, the product of a consanguineous marriage, who presented with a clinical picture of fish odor syndrome. The diagnosis was confirmed by detecting a mutation in the FMO3 gene through whole exome sequencing (WES).*

Result: *The constellation of clinical presentation, biochemical, and molecular genetics investigations showed a homozygous pathogenic variant in the FMO3 gene (OMIM: 136132), which is consistent with trimethylaminuria.*

Keywords
Trimethylaminuria, TMAU, FMO3 gene, Fish odor syndrome.

Introduction

Trimethylaminuria (OMIM: 602079) is a rare metabolic genetic disorder. The clinical presentation depends on the level of enzyme deficiency, which can range from complete to nearly complete. Symptoms often begin in childhood, but can develop as an adult as well. In this case, the main symptom is an offensive odor (fishy odor). Body fluids such as sweat, urine, breath, and other body fluids can give the fishy smell. There may be varying degrees of severity, and the odor often becomes apparent with sweating, stress, exercise, hormonal changes such as menstruation, and high dietary intake of trimethylaminuria precursors like eggs or fish. A person with this disorder often suffers from psychological problems, severe shame, anxiety, social isolation, low self-esteem, low confidence, frequent absences from school, and loneliness.

The main treatment for the disease involves limiting foods high in TMA precursors, such as eggs, liver, brassica vegetables, beans, peas, peanuts, and foods high in choline. In pediatric patients with documented biochemical deficiencies, riboflavin (Vitamin B2)

has been shown to enhance residual FMO3 activity and reduce TMA levels in some cases. In addition to antibiotics such as metronidazole or neomycin that reduce gut bacteria that produce TMA, activated charcoal or similar adsorbents may also be used to bind TMA to the gut. However, the evidence varies, and these interventions should be medically supervised.

Our case report describes a 10-year-old girl whose family noticed a fishy smell since she was a baby. There was no specific diagnosis made at any of the hospitals where she sought medical advice. The offensive fish odor gradually worsened and negatively affected the girl at school, both in front of her teachers and peers.

Method

Human Subject

Our study focused on a single affected individual (proband) from a Saudi-origin family. Various specialists - including a clinical geneticist, a general pediatrician, an endocrinologist, a gastroenterologist, and a metabolic consultant - conducted a comprehensive clinical evaluation of the patient.

Biochemical test

We have used tandem mass spectrometry (TMS) through dried blood spots (DBS) to identify metabolic, endocrine, and hereditary blood disorders. The test showed elevated trimethylaminuria level.

Molecular genetic test

Through DNA capture probes, fragmented genomic DNA can be enriched for target regions. A total of 41 Mb of human coding exome (targeting approximately 98% of the coding RefSeq from GRCh37/hg19) and the mitochondrial genome are included in these regions. An Illumina platform is used to sequence the generated library to achieve at least 20x coverage depth for more than 98% of the targeted bases. Bioinformatics pipelines are used to align reads with GRCh37/hg19 genomic assembly, the revised Cambridge Reference Sequence (rCRS) of Human Mitochondrial DNA (NC_012920), and call variants, annotate, and filter variants comprehensively. HGMD®, ClinVar, or CENTOGENE's own Biodatabank are used to evaluate variants with a minor allele frequency (MAF) less than 1%. In order to identify relevant variants, we focus on the coding exons and flanking 10 intronic nucleotides of genes with clear gene phenotype evidence (based on information from OMIM®). We consider all possible inheritance patterns. In addition, family history and clinical information are used to determine the pathogenicity and causality of identified variants. As per ACMG/AMP guidelines for variant classification and ClinGen recommendations, sequence variants are divided into five classes (pathogenic, likely pathogenic, VUS, likely benign, and benign). According to ACMG/ClinGen guidelines, CNVs fall into five categories: pathogenic, likely pathogenic, variant of uncertain significance [VUS], likely benign, and benign. Furthermore, risk factors and modifiers may be identified as clinically relevant variants. The patient's phenotype is reported along with all relevant variants. Upon detection of relevant variants by sequencing, CentoXome® MOx performs a biochemical analysis. As a result, metabolic disorders can be diagnosed earlier, variant classification optimized, and the eventual contribution to the phenotype can be determined. The list of enzyme activity assays and biomarkers can be found at www.centogene.com/mox. To ensure the quality of variants detected by NGS at CENTOGENE, a rigorous quality control process has been established. Orthogonal methods are used to confirm variants whose sequencing quality is low or whose zygosity is unclear. As a result, a specificity greater than 99.9% is ensured for all reported variants. Mitochondrial variants are reported for heteroplasmy levels of 15% or higher. This software detects copy number variation (CNV) with an accuracy of more than 95%. In uniparental dysomy (UPD) screening, well-known clinically relevant chromosomal regions (6q24, 7, 11p15.5, 14q32, 15q11q13, 20q13, and 20) are assessed using a specific algorithm.

Result

Tandem mass spectrometry showed elevated trimethylamine levels. Molecular genetic testing using whole exome sequencing (WES) identified a homozygous variant in the FMO3 gene, c.1139_1140del p. (Pro380HisfsTer3), which causes a frameshift starting at codon 380 in the exon(s). The resulting mRNA is predicted to undergo nonsense-mediated decay (NMD), and loss of function is a known disease mechanism for this gene. ClinVar lists this variant as pathogenic or likely pathogenic (Variation ID: 2961405). It is classified as pathogenic according to Centogene's implementation of ACMG/AMP/ClinGen SVI guidelines.

KFGH Case Report

We present a 10-year-old girl, the first child of healthy consanguineous Saudi parents from the Eastern Province, born in a private hospital. The mother reported no medical problems and no exposure to teratogens or alcohol. She had regular antenatal follow-up, which was reassuring.

At the age of 6 months, most family members noticed an offensive fish odor, which was unexplained to the family. They blamed the milk formula and changed it many times, but there was no benefit. They sought medical advice multiple times, but no definitive diagnosis was made. The problem was noticed by her teachers and classmates after she began attending school. Her peers often bullied her and she was socially isolated unintentionally. Physical examination showed a normal child with no dysmorphic features and normal growth parameters (weight 32 kg, height 146 cm, BMI 15 kg/m^2). She had normal development and average school performance. Other systemic examinations were normal. Initial laboratory workup showed a normal complete blood count, renal function, liver function profile, and thyroid function tests. Metabolic workup, including blood gases, serum ammonia, and serum lactate, were all within normal levels. Tandem mass spectrometry showed high trimethylamine, which was the clue to proceed with requesting Whole Exome Sequencing (WES), which detected a pathogenic variant in the FMO3 gene (OMIM: 136132).

Discussion

Trimethylaminuria is characterized by abnormal accumulations of volatile, malodorous trimethylamine in urine, sweat (ichthyohidrosis), and breath [1].

It was Humbert et al. who used the terms trimethylaminuria and fish odor syndrome for the first time in the case of a 6-year-old girl who had multiple infections of the lungs [2].

In 1976, Lee et al. observed two siblings who had trimethylaminuria; an offensive fish odor occurred when their mother was nursing them and had eaten eggs and fish [3].

A study by Zschocke et al. showed that FMO3 deficiency can cause an increased prevalence of hypertension and cardiovascular diseases, as well as abnormal drug metabolism [4].

According to Todd, affected patients have severe depression and even suicidal thoughts, as well as psychological difficulties at school [5].

Rehman reported a case with strong feelings of shame, embarrassment, low self-esteem, and social isolation. Rehman included in his article the importance of counseling, dietary adjustment, a short course of antibiotics, and gut adsorbents in management. Lifestyle changes, such as frequent body washing with soap with a pH of 5.5–6.6, also recommended by him [6].

Conclusion

Trimethylaminuria is a rare metabolic disease and an interesting condition to study until a definitive diagnosis is reached. We alert clinicians to consider the possibility of this inherited disease whenever there is an unexplained offensive fish odor. TMS and molecular genetic testing, specifically Whole Exome Sequencing (WES), are very helpful in reaching a definitive diagnosis and ruling out other differential diagnoses.

Finally, we emphasize the need for longitudinal data and clinical trials in management to decrease the impact of the disease on psychological and social well-being. Future research is needed to elucidate the long-term outcomes for these patients.

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