Intestinal Metabolic Bromhidrosis Syndrome (IMBS)

Doctor's Guide

Introduction

Intestinal Metabolic Bromhidrosis Syndrome is characterized by patients having chronic body odor in general (with or without bad breath).

The medical term for body odor is called **Bromhidrosis** and the term for bad breath is called **Halitosis**.

The Bromhidrosis and Halitosis for IMBS patients is caused by **odorous intestinal metabolites passing the intestinal barrier and the liver** to be excreted by **skin glands** (Bromhidrosis) or the **lung gas exchange** (Halitosis).

Regularly the body odor of IMBS patient is **recognized** as way **more pungent or "room filling"** compared to normal body odor that is caused by weak hygiene.

Also, its important to note that IMBS patients despite their strong and pungent body odor have no been recognized to be presented with any hygiene issues. In fact (over) increased hygiene will normally not have any beneficial effect.

Different types of Bromhidrosis (and Halitosis)

As IMBS patients share the aspect of having chronic Bromhidrosis, patient individual smell types will differ with a great variation.

Following smell types are known, but there may be further not yet documented types:

- Fecal like body odor and halitosis (Indole, Skatole)
- Sweat like, sweaty feet and vomit like body odor (Carboxylates, e.g. Butyrate, Isovalerate, …)
- Urine like body odor (Ammonia)
- Rotten or foul eggs like body odor and halitosis (Sulfides)
- Rotten meat like body odor and halitosis (Putrescine)
- Rotten or dead fish like body odor (Trimethylamine)
- Cabbage like body odor and halitosis (Methanethiol)

In brackets the likely affected intestinal metabolites are mentioned. For patients with e.g. impaired mitochondrial activity it is also common that multiple metabolites are affected, so the odor type can change based on the diet.

Differences in phenotype intensity

It is possible that IMBS patients do only show a single body odor or halitosis type, but also a large part of the patients does report various body odors that are influenced by:

- Diet
- Menstrual cycle

- Stressful events
- Exercise

As a doctor it is important to know that there are **mild** as well as **severe** cases. In the severe cases the doctor might be able to have an immediate olfactory perception of the bromhidrosis symptoms. For the mild cases a direct olfactory evaluation might be compromised by facts like:

- **triggering foods** have to be consumed by the patient 6-24h before
- some odors especially from the methanethiol and indole type are known to accumulate in the whole room which can be **less perceivable in an air conditioned environment**
- odors from the carboxylic type are based on salt excretion from the skin. Those odorous organic salts can **accumulate in clothes** and are odorless in dry state. Those accumulated salts are partially not removable by washing detergents and can be reactivated to emit a strong odor when exposed to water steam

In severe cases we propose also to have a disposable chemical resistant coverall (e.g. DuPont™ Tychem® coverall) in largest size available for the patient, which can be worn over the normal clothes. If the patient choses to wear protection clothes, this can have the advantage that the patient feels more comfortable being close to other patients and other patients will have a less irritations as some of the excreted odorous metabolites in IMBS patients can be highly intense.

Diagnostic

At this point in time official medical diagnostic is only available for three primarily odor related diseases:

- Trimethylaminuria (TMAU) [1] [2] [3]
  - TMAU urine test (Trimethylamine to Trimethylamine N-oxide ratio)
  - Genetic test for FMO3 gene defects
- Dimethylglycinuria [4] [5]
  - Urine test (Dimethylglycine)
  - Genetic test for DMGDH gene defects
- Methanethiol oxidase deficiency (EHMTO) [6] [7]
  - Genetic test for SELENBP1 gene defects

Additionally, **weak urea cycle disorders** can be the cause of a failure of the mitochondrial function in the intestinal barrier (without any other typical phenotype), which regularly leads to elevated **ammonia, ornithine, glycine, glutamine** blood levels after a protein rich diet and which results in a carboxylate/short chain fatty acid (sweaty, vomit, sweaty feet, …) and ammonia (urine) driven body odor.

Despite the fact, that **regular standard blood and urine tests** do **not show any noticeable hints** in most IMBS cases, in **explorative** investigations there have been **various blood and urine markers** found to be out of normal range.

[1] https://omim.org/entry/602079
[2] https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3848652/
[3] https://doi.org/10.1016/j.drudis.2020.06.026
[4] https://www.omim.org/entry/605850
[5] https://www.metagene.de/diseases/DIMETHYLGLYCINURIA(DMGDHD).html
[6] https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5742538/
[7] https://www.omim.org/entry/618148

The closest related disorders are the classical **urea cycle** and **organic aciduria disorders** and **Irritable Bowel Syndrome (IBS)**.

Important is to notice that **classical organic acid urine screenings** are normally **not able to reveal diagnostic relevant information** in IMBS patients.

In classical organic acidurias the underlying enzyme deficiencies are present in all organ cells, so that direct affected metabolites are easily to be identified in urine screenings.

In IMBS patient cases similar effects are present but **localized to the cells of the intestinal barrier or liver** cells. This circumstance leads to the situation that locally elevated metabolites are degraded quickly by the liver and kidney metabolism and are therefore **masked in the urine test**.

In general are **blood tests more likely to reveal direct affected metabolites** than urine tests, especially after a **provocation diet**.

Metabolome blood test

Ammonia blood test

A blood test for **hyperammonemia** is recommended after a **protein rich diet** (red meat, chicken, lenses, …) over **multiple days** upfront the test.

As **precaution**, if a very **prominent urine like body odor** is already present, it is also recommended to execute **two cycles** of blood ammonia test, the **first** one directly **without any protein load** and only the **second test cycle with a protein load**, if the first test did not reveal elevated levels. Hyperammonemia can be life threatening and a protein load can cause **irreversible nerve damage** in certain edge cases.

Amino acid blood test

An amino acid blood test can reveal elevated amino acid levels for

- Tryptophan
- Glycine
- Serine
- Glutamine
- Glutamate
- Ornithine
- Citrulline
- Taurine
- Threonine

Especially elevated **ornithine or citrulline markers** should be investigated carefully. Elevated ornithine and citrulline levels, especially with elevated glycine or glutamine/glutamate levels, **can indicate high local ammonia levels** in the intestinal barrier cells (even if ammonia levels are still in normal ranges).

Especially if only the slightest **constipation** or **IBS-C** symptoms are present with any sign of loss of nerve function in the large colon, a standard **hyperammonia treatment with sodium benzoate** (max 5g oral in water solution and distributed over the day for about one week) might be an appropriate treatment choice.

Urine metabolome test

In the urine metabolome following markers can be present. Always be aware that markers can **highly fluctuate** based on **diet** within the last 24h.

- Benzoate

- Hippurate
- Dimethylglycine
- Glycine
- Ornithine
- Citrulline
- Homovanillate
- Hydroxymethylglutarate
- Para-hydroxyphenylacetate
- beta-alanine
- Anserine
- Carnosine
- Methylmalonate

Other blood tests

- Parathyroid hormone (PTH)
- Potassium (low)

Genetic test

Genetic tests have **limited** information at the moment. But it is worth mentioning that the intestinal lining and the liver express enzymes like the EC .6.2.1.2 (butryate CoA ligase).

The EC 6.2.1.2 is encoded by multiple genes like e.g. the ACSM2B and is responsible for **butyrate** and **hexanoate** degradation and to a lesser extend also for the **benzoate degradation**.[8]

For those gene groups there are no clinical variants known at the moment, but still the raw data of an exome tests for those genes might contain relevant information which the patient can reevaluate in the future using designated private service providers.

For a **current set of gene candidates** please contact support@imbs-alliance.org or view the 'gene candidate' section on the www.imbs-alliance.org website.

Treatment

At this point in time official treatment options for chronic body odor underlying diseases are limited.

Trimethylaminuria

- Choline, Betaine, Lecithin, Carnitine reduced diet
- Riboflavin supplementation[9]
- Non resorbable antibiotics

Hyperammonemia / Weak urea cycle disorders

- Sodium benzoate + sodium phenylbutyrate
- Protein reduction diet
- Magnesium oxide + sodium hydrogen carbonate

[8] https://www.uniprot.org/uniprot/Q68CK6
[9] https://doi.org/10.1016/j.drudis.2020.06.026

Patient organizations/support groups

Currently known patient support groups are the following:

- IMBS Alliance (www.imbs-alliance.org)
- MEBO (www.meboresearch.org, www.meboresearch.co.uk and www.meboblog.com)

Community

- RareConnect (www.rareconnect.org)
  IMBS (https://www.rareconnect.org/en/community/imbs)
  Trimethylaminuria (https://www.rareconnect.org/en/community/trimethylaminuria)

Contact and feedback

If patients or doctors need first support where to find information around this disease and/or related patient communities do not hesitate to contact:

support@imbs-alliance.org

Any feedback (critic, improvement suggestions, …) around this guide is welcome and can be sent to the following email address: feedback@imbs-alliance.org