

AN OVERVIEW OF UNUSUAL AND RARE DISEASE: AUTO-BREWERY SYNDROME

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Abstract:

Auto-brewery syndrome, also known as gut fermentation syndrome, is a fascinating condition where ethanol is produced internally through fermentation by fungi or bacteria in various parts of the body, such as the gastrointestinal system, oral cavity, or urinary system. Patients with autobrewery syndrome exhibit various signs and symptoms of alcohol intoxication, despite claiming to have not consumed any alcohol. They frequently mention following a diet that is rich in sugar and carbohydrates. Endogenous ethanol is produced in small amounts during normal digestion. However, if fermenting yeast or bacteria become pathogenic, it can lead to dangerously high blood alcohol levels. Auto-brewery syndrome is more commonly found in patients who have other medical conditions like diabetes, obesity, and Crohn disease. However, it can also affect individuals who are otherwise healthy. Various strains of fermenting yeasts and uncommon bacteria are recognized as pathogens. Auto-brewery syndrome is a condition that is not frequently diagnosed, but it is likely that it is not being diagnosed as often as it should be. Two extremely rare cases of auto-brewery syndrome have been identified, one in the oral cavity and one in the urinary bladder. This article primarily discusses the causes, symptoms, tests, treatment, and legal aspects of ABS.

Keywords: Alcohol; Diabetes mellitus; gut fermentation; Stress; obesity

Introduction:

Auto-brewery syndrome (ABS), also known as gut fermentation syndrome, is a condition in which the body's ethanol concentration increases significantly even with minimal or no alcohol consumption [2]. It's a condition that typically impacts individuals who already have underlying gut problems [2,3]. This intriguing phenomenon is thought to be caused by the breakdown of carbohydrates in the human body by microorganisms [3]. The pharmacokinetics of alcohol can be influenced by various factors [4]. Prior to the accumulation of ethanol in the body fluids, it is crucial for the amount of ethanol in the body to surpass 6 to 8 g per hour as a result of first-pass metabolism [5,6]. The available data does not provide enough evidence to support the widespread production of ethanol through natural processes. Nevertheless, this intriguing occurrence has given rise to many misunderstandings and untrustworthy data that could be

manipulated for legal and medical purposes [6]. This review article aims to improve understanding of this rare condition by analyzing the findings of various case reports and studies. This article provides a thorough overview of the different presentations of ABS and offers practical strategies for effective management.

Etiology:

Certain yeasts from the *Candida* and *Saccharomyces* families can transition from harmless commensals to pathogenic organisms, leading to the development of auto-brewery syndrome. Some bacteria strains are capable of fermenting ethanol.

- Various strains of yeasts, including *Saccharomyces cerevisiae*, *S. boulardii, and different types of Candida like C. glabrata, C. albicans, C. kefyr, and C. parapsilosis*, have been identified as potential causes of this condition [7].
- *Klebsiella pneumonia, Enterococcus faecium, E. faecalis, and Citrobacterfreundii*bacteria have been found to be involved in at least one case each [8-10].
- Certain medical conditions, like diabetes or liver problems, may affect the diagnosis of ABS. Individuals diagnosed with type 2 diabetes mellitus (DM) or liver cirrhosis (LC) exhibited elevated levels of endogenous ethanol (EnEth) compared to a control group without these conditions. However, the EnEth levels reached their highest point in a specific group of patients who had both type 2 DM and LC. In this group, the blood alcohol concentration reached 22.3 mg/dL [11].
- Four common yeasts (*Candida albicans, Candida tropicalis, Saccharomyces cerevisiae, and Torulopsisglabrata*) were mixed with infant formulas. The production of ethanol was measured at both the 24-hour and 48-hour marks. The quantities of ethanol produced provide a possible explanation for patients who display symptoms of auto-brewery syndrome [12].
- EnEth plays a role in the development of non-alcoholic fatty liver disease (NAFLD) through bacterial production [13,14]. Obese patients and those with non-alcoholic steatohepatitis (NASH) also show higher levels of EnEth [15-18].

Epidemiology and patient characteristics:

ABS is becoming increasingly popular among people of all ages and genders. A study conducted in the United Arab Emirates (UAE) by Al-Awadhi *et al.* aimed to highlight the natural levels of blood ethanol in different subsets of the population. There were no significant differences found among the participants in terms of age, gender, and nationality [19]. In a study conducted by Ragab*et al.*, similar findings were observed in the population of Saudi Arabia [20]. A study conducted by Nair *et al.* found that individuals who were obese and females with non-alcoholic steatohepatitis (NASH) exhibited elevated levels of breath alcohol concentration. Nevertheless, the disparity among females did not show any statistical significance [21]. A study conducted by Iizumi*et al.* examined 52 diagnosed cases of ABS and revealed significant differences in the health status and daily life activities between the two groups. The variation in gastrointestinal motility, liquid intake, and food sensitivities was quite evident. According to the study, it was noted that the patients in the ABS group had worse health, had more frequent bowel movements, were more sensitive to foods, drank more water, and avoided starch-containing products [3].

Pathophysiology:

Understanding the underlying mechanisms of disease ABS arises from the extensive growth of gut microorganisms, resulting in the production of ethanol within the body. This phenomenon is commonly associated with the consumption of meals high in carbohydrates or the use of antibiotics, both of which can disrupt the balance of the gut ecosystem [2,22]. It is often linked to underlying pathology. In a study conducted by Hafez *et al.*, it was found that diabetic patients had significantly higher concentrations of ethanol ($4.85 \pm 3.96 \text{ mg/dL}$) compared to the control group ($0.3 \pm 0.41 \text{ mg/dL}$) [23]. In the same vein, individuals with liver cirrhosis also exhibited higher levels of ethanol ($3.45 \pm 2.65 \text{ mg/dL}$). In addition to being observed in patients with other disorders such as Crohn's disease, short bowel syndrome, and chronic intestinal pseudo-obstruction [24-27], this syndrome is also commonly seen. Additional research is necessary to investigate the link between ethanol production and metabolism rates and ABS. These rates can differ among various groups of people due to factors like diet and genetic variations in the aldehyde dehydrogenase enzyme [2,6,28].

Clinical presentation:

Patients with ABS typically exhibit symptoms similar to those of alcohol intoxication. These encompass a range of abnormalities, such as those affecting the neurological, gastrointestinal, respiratory, and psychological systems. Neurologic symptoms commonly found in the literature encompass seizures, slurred speech, lack of coordination resulting in falls, blurred vision, dizziness, and memory impairment [29-31]. The gastrointestinal abnormalities consist of symptoms such as nausea, vomiting, diarrhea, and general abdominal discomfort [32,35]. Psychological disorders such as depression, unusual behavior, sleepiness, confusion, tiredness, and mental disarray are frequently linked to it. Some patients may experience respiratory symptoms like a runny nose and cough [36-38]. Given the variety of non-specific signs and symptoms, it is crucial to consider other possible causes, such as head trauma, excessive alcohol consumption, lactic acidosis, and various psychiatric disorders [39].

Diagnosis:

Patients may not initially exhibit signs of intoxication, but they may experience neurological symptoms, coordination difficulties, and changes in mood. Auto-brewery syndrome should be taken into account when evaluating patients with a high blood alcohol level who claim to have not consumed any alcohol, even in cases of DWI arrests [40].

Patients with chronic intestinal obstruction, gastroparesis, diabetes, or liver dysfunction such as non-alcoholic fatty liver disease (NAFLD) or nonalcoholicsteatohepatitis (NASH) are at a higher risk of developing auto-brewery syndrome. It is important to take an interprofessional approach that includes a psychiatric evaluation.

It is important to consider the following factors during the evaluation:

- a) Perform a thorough history and physical examination, including gathering information from family members about diet, alcohol consumption, and any instances of unexplained intoxication.
- b) Conduct laboratory tests, including a complete blood count, metabolic panel, blood alcohol level, drug screen, and stool culture and sensitivity tests for both bacterial and fungal infections.
- c) Rule out other potential underlying causes, such as head injury, hidden alcohol consumption, or psychiatric conditions.
- d) A 24-hour study involving the consumption of a high carbohydrate diet and a carbohydrate challenge of 200g glucose. BAC and BrAC testing will be conducted at intervals of 0, 1/2, 1, 2, 4, 8, 16, and 24 hours. If the levels are elevated during the test, it will confirm the presence of auto-brewery syndrome.
- e) Performing upper and lower endoscopy with samples for culture and sensitivity (bacterial and fungal) [40].

It's important for clinicians to note that the occurrence of an episode (or flare) within 24 hours can vary depending on factors such as transit time and the presence of fermenting microbes in different locations.

Treatment / Management

A well-rounded treatment program should involve the patient's input to ensure compliance.

- a) **Immediate Care:** The patient displaying a significantly elevated blood alcohol level should receive treatment for acute alcohol poisoning and be stabilized.
- b) **Prescribing drug therapy:** Administer medication based on culture and sensitivity results for the identified yeast or bacteria. Typically, patients need to undergo a series of treatments involving the use of azoles or polyenes. For rare or resistant microbes, an echinocandin or an antibiotic is necessary.
- c) **Diet therapy:** For the effective management of auto-brewery syndrome, it is crucial to make dietary adjustments that involve consuming high protein and low carbohydrates until the symptoms diminish. When sugar is fermented, it turns into alcohol. By following a diet that excludes both simple and complex sugars, you can reduce the amount of alcohol that is produced in your gastrointestinal and genitourinary tract.

d) **Supplements:**Multistrain probiotic supplements can help restore bacterial balance in the gastrointestinal tract and have shown potential in addressing auto-brewery syndrome, although further research is needed to confirm their efficacy as a treatment.

To reduce the chances of a relapse in auto-brewery syndrome, it is advisable to steer clear of consuming carbohydrates. It is important to have a nutritionist involved in the treatment and management of the disease.

Anything that disrupts the delicate balance of bacteria in the gut can potentially lead to increased fermentation. It is advisable to minimize the use of antibiotics whenever feasible. If a course of antibiotics is necessary, it is important to have a plan in place to retest for fermenting pathogens and provide treatment if needed.

Through different approaches, such as managing carbohydrate intake, utilizing antifungal or antibiotic treatments, minimizing antibiotic usage, and incorporating probiotics, various methods have shown promising results. However, patients experiencing persistent, recurring episodes may benefit from fecalmicrobiota transplants [41].

Prognosis

Certain patients may find relief from symptoms of auto-brewery syndrome by discontinuing antibiotics and adopting a sugar-free, low-carbohydrate diet [42]. Some individuals may need antifungals or antibiotics, in addition to making changes to their diet. Using probiotics, following a low carbohydrate diet, and being cautious with antibiotics can be beneficial in preventing relapse. Some patients experience persistent relapses and struggle to maintain a healthy microbiome, leading to recurring episodes of intoxication.

Complications

After one treatment, patients can typically resume their normal diet and lifestyle. Some patients may experience relapses, particularly if they are prescribed antibiotics that disrupt the balance of bacteria in the gut. Nevertheless, Auto-brewery syndrome can greatly impact patients and their families. Auto-brewery syndrome is often misinterpreted as alcohol consumption, leading to various social and legal complications. ABS can have a significant impact on individuals and their relationships, causing stress for all parties involved.

Even after symptoms have subsided, prolonged exposure to endogenous ethanol can lead to a strong desire for and dependence on alcohol, leading to subsequent drinking. Alcohol use disorder may develop during or after treatment [43].

Relation with drugs

An intriguing connection between cimetidine and ethanol production in the stomach was shown by Bode *et al.* The participants who were given either cimetidine or antacids showed elevated ethanol levels in the gastric juice compared to the other group. Further evidence is needed to evaluate the exact cause, but the drugs caused a change in pH that resulted in the growth of microorganisms, ultimately leading to ethanol production [44].

Medicolegal aspect

The legal implications of ABS syndrome are a captivating yet controversial topic in the field of forensic medicine. There have been instances where the accuracy of BAL and breath alcohol levels has been called into question during court cases. The defense often argues that ABS syndrome can naturally produce alcohol, raising doubts about the results. Numerous studies have been conducted to demonstrate the average levels of alcohol that can be produced in the body. The levels were detected in various bodily fluids such as blood, urine, and plasma, as well as breath, using highly sensitive tests like gas chromatography and enzymatic oxidation. According to these studies, it is very rare for the body to produce high levels of alcohol (>80 mg/dL) through ABS syndrome, although a small amount of alcohol can be produced. The correlation between diabetes mellitus and the body's natural production of ethanol was examined in a study conducted by Simicet al. The BAL levels in the diabetic group were found to be significantly higher compared to the control group (2.65 mg/dL vs 0.40 mg/dL) using the headspace gas chromatography method (HS-GC). The Widmark method, a less specific test, showed a higher average value of 27.28 mg/dL in diabetic patients. However, it is still significantly lower than the levels linked to illegal intoxication. The urine alcohol levels in the diabetic group were found to be significantly higher (6.13 mg/dL vs 3.27 mg/dL) according to the HS-GC method of measurement. The values between the diabetic and control group showed significant differences according to Widmark's method (54.27 mg/dL vs 8.30 mg/dL) [45]. On the other hand, a study conducted by Alexander et al. in 1988 compared the urine ethanol levels of 10 diabetic patients with the urine of a healthy volunteer. The gas-liquid chromatography results indicated initially low ethanol levels. On the third day, one patient in the study experienced a substantial increase in ethanol levels, reaching about 700 mg/dL. This trend was observed over a three-week period, specifically among diabetic patients [46]. Several instances described in the literature have revealed the presence of a notable BAL level, leading to the emergence of symptoms associated with intoxication. Considering the various findings in the literature, additional research is required to reach a conclusive decision on this matter.

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