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AN OVERVIEW ON AUTO BREWERY SYNDROME

Rachamsetty kavya[1], V.Keerthireddy[2], D.Pavithra[3], Dhachinamoorthi Duraiswamy [4] , Rama Chandra Reddy Linga[5]

[1] Assistant professor, Department of pharmacy practice, QIS College of Pharmacy, Ongole ,Andhra Pradesh

[2,3] Pharm.D ,QIS College of Pharmacy ,Ongole ,Andhra Pradesh [4] Principal ,Qis College of Pharmacy ,[5] HOD Of pharmacy practice , QIS College of Pharmacy ,Ongole

Abstract:

Auto-brewery syndrome (ABS), also known as gut fermentation syndrome, which is rare disorder. It is characterized by the endogenous production of alcohol that typically presents with the signs of alcohol intoxication, such as staggering gait, slurred speech, gastrointestinal distress, and state of confusion. Due to the nonspecific symptoms, it is necessary to rule out other etiologies before diagnosis of ABS. The confirmatory test for this syndrome is the raised levels of blood or breath ethanol after a glucose challenge test. The management includes the use of antifungal drugs and avoidance of a carbohydrate-rich diet. In this review, we summarize the etiology, clinical presentation, diagnostic tests, management, and medicolegal aspects of ABS.

Keywords: Auto brewery syndrome, Ethanol, Gut fermentation.

Introduction:

Patients with Auto-Brewery Syndrome (ABS), also called gut fermentation syndrome, experience alcohol intoxication following consumption of a high-carbohydrate, alcohol-free diet[1-2]. The first reports of ABS instances date back to 1894 and were published in the French-English book Auto-Intoxication in Disease in 1906[3]. Since then, more cases of ABS have been reported, with the majority of these cases being caused by Candida and Saccharomyces species (Candida albicans, Candida krusei, Candida glabrata, Candida intermedia, Candida parapsilosis, Candida kefyr, and Saccharomyces cerevisiae). The authors of these reports have assumed that the causative organisms may ferment carbohydrates into excess alcohol in the gut, resulting in a state of inebriation. Small amounts of endogenous ethanol are typically produced inside cells as products or intermediates in metabolic processes. Pyruvate from carbohydrates can be converted into acetaldehyde in the colon's anaerobic environment, and acetaldehyde can subsequently be reduced to generate ethanol[11,12]. This mechanism is favored in cases of intestinal yeast or bacterial overgrowth and high carbohydrate ingestion[13]. The intestinal and liver alcohol dehydrogenases (Adh),

catalases, and the microsomal ethanol-oxidizing system swiftly and nearly entirely eliminate the resulting endogenous ethanol from the blood. Still, endogenous ethanol will build up in the body and cause elevated blood alcohol concentration (BAC) and the onset of ABS if it surpasses the intestine's and liver's metabolic capacity.

Previous reports have suggested that ABS may be caused by abnormal yeast overgrowth [4–10]. However, these studies were mostly based on stool tests for yeast overgrowth and empiric therapy. Indeed, due to the complex gut microbiota, potential pathobionts are likely to be overlooked. It is known that intestinal dysbacteriosis is associated with various chronic diseases [14–17] ,and the overgrowth of certain bacteria capable of producing alcohol in the intestine may also play an important role in ABS. We recently described a patient with severe nonalcoholic steatohepatitis (NASH) associated with high alcohol (HiAlc) K. pneumoniae ABS that produced large amounts of endogenous alcohol and was unresponsive to antifungal drugs about the patient's symptoms[18]. Thus, it is reasonable to hypothesize that HiAlc K. pneumoniae is the causative agent of bacterial ABS. However, the detailed pathogenesis of HiAlc K. pneumoniae and the role of this pathobiont in the progression of ABS, especially regarding the dynamic changes of gut microbiota, have not been fully elucidated. Our preliminary findings indicate that further evidence is needed to support the role of HiAlc in Klebsiella of ABS progression in a cohort that can guide clinical management.

During the last 3 decades, most cases of ABS have been reported anecdotally [1–4]. To our knowledge, there are no clinical consensus guidelines on gut microbiota changes and treatment of bacterial ABS. Most patients are treated with a controlled diet or empiric antifungal therapy [4-6,8-10,19,20]. Despite the need for evidence-based ABS therapy, differences in the intestinal microflora of affected patients have not been fully described. Based on previous studies, we hypothesize that some bacteria, such as Klebsiella, play an important role in the pathogenesis of ABS. These bacteria growing in the intestines of ABS patients can produce large amounts of endogenous ethanol, which causes intoxication in the patient. Targeted use of antibiotics to the microbiota can effectively control the clinical symptoms of ABS patients unresponsive to antifungal therapy. To confirm this hypothesis, we conducted this study in a clinical cohort.

BACKGROUND

The consumption of alcoholic beverages is as old as human history and originates from early civilizations such as Ancient Egypt and Ancient China [21]. Alcoholic distillation can be associated with the early scholars of the Islamic world [22]. Ethanol alcohol. beverages are among the most widely used and accepted in the world.[23]. Excessive consumption of alcoholic beverages has negative medical and social consequences. However, some people can suffer these effects without consuming alcohol. These unfortunate individuals suffer from Gut Fermentation Syndrome (GFS), also known as Endogenous Alcoholic Fermentation Syndrome, Gut Fermentation Syndrome, or Homebrew Syndrome [24]. GFS is a rare and little known disease. Fungi and/or bacteria in the digestive tract metabolize the consumed carbohydrates into alcohol. Fungi are not normally found in the upper gastrointestinal tract [25], but may be present in the colon as part of the commensal microbiome. It is known that some fungi produce ethanol, for example fungi belonging to the families Candida and Saccharomyces [26]. Recently, the role of bacteria, including Klebsiella

and Escherichia, has been revealed in the production of intestinal alcohol[27,28]. Several factors affect the pharmacokinetics of alcohol [29]. Ethanol undergoes primary metabolism before entering the bloodstream; Therefore, the amount of ethanol in the body should exceed 6-8 g per hour before it begins to accumulate in body fluids [30,31]. The endogenous production of ethanol in such large quantities is not supported by sufficient data, but the novelty of this unique phenomenon has created many misunderstandings and unreliable information that can be manipulated for medically legitimate purposes [31].

ETHANOL FORMATION BY ETHANOL-PRODUCING MICROORGANISMS:

There are several steps in the glucose fermentation process before ethanol is formed in fungi and bacteria. First, a hexose transporter transports glucose into the cell, after which hexokinase phosphorylates it to glucose-6-phosphate. Phosphohexoisomerase converts it to fructose-6-phosphate. Fructose-6-phosphate is phosphorylated by phosphofructokinase-2 to fructose-1,6-bisphosphate, which is then converted to glyceraldehyde-3-phosphate by aldolase. The latter is converted to 1,3-bisphosphoglycerate by glyceraldehyde-3-phosphate dehydrogenase. This 1,3-bisphosphoglycerate is converted to pyruvate in several steps. Pyruvate is converted to acetaldehyde by pyruvate decarboxylase, which is then converted to the final product ethanol by alcohol dehydrogenase (see figure 1).

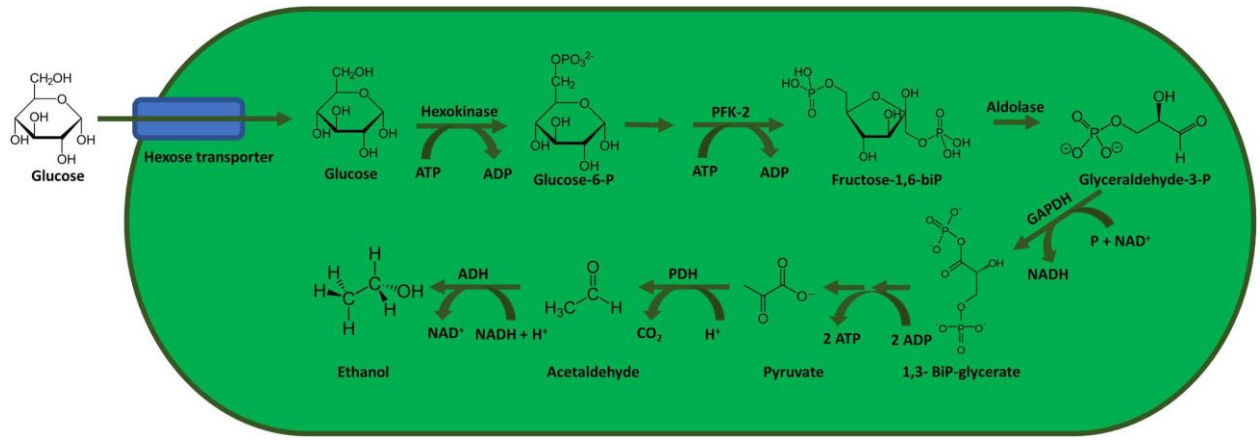

FIGURE 1 Fungal and bacterial fermentation process of the metabolism of glucose to ethanol. ADH, alcohol dehydrogenase; ADP, adenosine-diphosphate; ATP, adenosine-triphosphate; GAPDH, glyceraldehyde-3-phosphate dehydrogenase; NAD+, nicotinamide adenine dinucleotide; P, phosphate; PFK-2, phosphofructokinase-2; PHD, pyruvate decarboxylase.

MICROORGANISMS ASSOCIATED WITH GFS:

Eighteen of 20 case reports described different microorganisms causing GFS. Species included K. pneumoniae, C. albicans, C. glabrata, S. cerevisiae, C. intermedia, C. parapsilosis and C. kefyr. One study mentioned that they found Pseudomonas in a duodenal aspirate [32]. Pseudomonas is rarely present in the microbiome; however, coinfection between Pseudomonas and C. families are relatively common. Ethanol production by C. albicans strongly influences the formation of a biofilm of P. aeruginosa and the production of phenazine [33]. However, in the case described by Akbaba et al[32], no fungal organisms were found in the mushroom culture. The diagnosis of GFS was made after the carbohydrate challenge test was positive but the causative microorganism was not identified.

PATHOPHYSIOLOGY:

ABS is caused by an overgrowth of intestinal microorganisms, which in turn leads to the production of endogenous ethanol. This phenomenon is usually preceded by the consumption of carbohydrate-rich meals or the use of antibiotics, which can disturb the intestinal ecosystem [34,35]. Often it is also related to the underlying pathology showed a significantly higher ethanol concentration in diabetics (4.85 ± 3.96 mg/dl) and cirrhotic patients (3.45 ± 2.65 mg/dl) than in controls (0.3 ± 0.41 mg/dl) [36]. This syndrome has also been found in patients suffering from other diseases such as Crohn's disease, short bowel syndrome and chronic intestinal pseudo-obstruction [37-40]. Although ethanol production and metabolic rates may differ in different population subgroups due to dietary variation and genetic polymorphism of the aldehyde dehydrogenase enzyme, its association with ABS requires further investigation [34,41,42].

1.Alteration of the gut microbiome:

The disruption of gut homeostasis resulting in overgrowth of fungi, and in rare cases, high alcohol-producing bacteria (e.g., Klebsiella species).1,10 All of our patients had prior exposure to antibiotics before developing ABS symptoms.

2. Fungal fermentation:

Commercially, Saccharomyces cerevisiae (i.e., brewer’s yeast) has been used for manufacturing beer for centuries

Risk Factors:

The most frequent risk factor for its pathogenesis in our ABS patient population has been previous antibiotic use. Yeast overgrowth may have resulted from antibiotics upsetting the delicate homeostatic balance and symbiotic connection between the various gut microbiota species. There have also been reports of ABS in a number of patients with intestinal bacterial overgrowth, diabetes, short bowel syndrome, and inflammatory bowel illness (Crohn's disease with strictures). In healthy individuals, exposure to a precipitating factor may also result in ABS.It's unclear if these people were predisposed to ABS by any hereditary factors.

SYMPTOMS:

It is common for patients with ABS to exhibit signs and symptoms of intoxication. Some with neurological symptoms (drowsiness, brain fog, seizures, ataxia), or psychological symptoms (adjusted mood, anxiety, dysphoria, changes in emotion, and sadness). Alcohol odors may also be detected on the patients' breath. Whether alcohol is obtained endogenously or exogenously, it has the same effects and raises the risk of cirrhosis of the liver, fatty liver, and acute or chronic pancreatitis.10 In many places, including New York, the legal limit for driving while intoxicated (DWI) is 0.08%. Many patients with ABS who had three to four times this level have been seen by us. Additionally, these symptoms may coexist with those of chronic fatigue.

TREATMENT / MANAGEMENT:

The same initial treatment protocol used for exogenous alcohol intoxication should be used to treat ABS patients as well. This would include administering appropriate intravenous fluids for hydration, maintaining a clear airway, and correcting calorie and nutritional deficiencies (folate and thiamine). Alcohol withdrawal symptoms if present should also be managed with benzodiazepines. After the resolution of the patient's acute symptoms and stabilization of the patient's condition, targeted treatment for the patient's ABS can be initiated.

• **Drug therapy**: Determine drug therapy for the identified yeast or bacteria based on culture and sensitivity results. Most patients require one or more courses of azole or polyene therapy. Rare or resistant microbes require an echinocandin or antibiotic.

• **Diet therapy**: The essential treatment for Autobrewery syndrome is a change in diet that requires high protein and low carbohydrates until the symptoms disappear. Sugar is fermented into alcohol, and a diet that eliminates simple and complex sugars reduces the amount of alcohol fermented in the digestive tract and urinary tract.

• **Dietary supplements**: Multi-probiotic supplements help balance bacteria in the digestive tract and have been used to treat auto brewery syndrome, but have not yet been studied as a treatment.

The risk of recurrence of auto brewery syndrome is reduced by avoiding carbohydrates. A nutritionist should be involved in the treatment and management of the disease. Anything that creates an imbalance between harmful and beneficial bacteria can potentially increase fermentation in the gut. Antibiotics should be avoided if possible. If a course of antibiotics is required, a plan should be made to retest for yeast pathogens and treat if necessary. Dietary carbohydrate control, antifungal or antibiotic therapy, general antibiotic avoidance, and probiotics have been reported to be successful treatments alone and in various combinations. However, patients with long-term chronic exacerbations may require fecal microbiota transplantation [43].

CONCLUSION:

ABS is a rare and underdiagnosed medical condition where ingested carbohydrate is converted to alcohol by fermentation in the gut. This condition should be considered in any patient who has signs and symptoms of inebriation despite denying alcohol intake. This syndrome has been described in the medical literature for over 50 years, but it still remains a condition with limited information regarding diagnosis and treatment. If a physician suspects that a patient has ABS, breathalyzer analysis during the symptomatic episodes could help the clinician determine if this condition might be present. We propose a standardized carbohydrate challenge test to screen patients with suspected diagnosis of ABS. While a positive test is very useful in detecting patients with ABS, a negative test does not definitively rule out ABS, as fungi could take longer than 24 hours to convert carbohydrate to alcohol. The seminal NIH microbiome study from 2007 using genetic methodology has found many fungi are undetected by our usual commercial laboratory culture techniques.15,17 As more research emerges on the gut microbiome, it is hoped that a better understanding of this medical condition will ensue.

REFERENCES:

1 Iwata K. A review of the literature on Drunken syndromes due to yeasts in the gastrointestinal tract. Tokyo: University of Tokyo Press; 1972:260–268.

2 Kaji H, Asanuma Y, Ide H, et al. The auto-brewery syndrome–the repeated attacks of alcoholic intoxication due to the overgrowth of Candida (albicans) in the gastrointestinal tract. Mater Med Pol. 1976;8(4):429–435.

3 Bouchard Ch. Lectures on autointoxication in disease, or selfpoisoning of the individual. J Am Med Assoc. 1906;xlvi(4):148.

4 Kaji H, Asanuma Y, Yahara O, et al. Intragastrointestinal alcohol fermentation syndrome: report of two cases and review of the literature. J Forensic Sci Soc. 1984;24:461–471.

5 Dahshan A, Donovan K. Auto-brewery syndrome in a child with short gut syndrome: case report and review of the literature. J Pediatr Gastroenterol Nutr. 2001;33:214–215.

6 Jansson-Nettelbladt E, Meurling S, Petrini B, Sjolin J. Endogenous ethanol fermentation in a child with short bowel syndrome. Acta Paediatr. 2006;95:502–504.

7 Cordell B, McCarthy J. A case study of gut fermentation syndrome (auto-brewery) with Saccharomyces cerevisiae as the causative organism. Int J Clin Med. 2013;4:309–312.

8 Cordell B, Kanodia A. Auto-brewery as an emerging syndrome: three representative case studies. J Clin Med Case Rep. 2015;2:1–5.

9 Saverimuttu J, Malik F, Arulthasan M, et al. A case of auto-brewery syndrome treated with micafungin. Cureus. 2019;11:e5904.

10 Malik F, Wickremesinghe P, Saverimuttu J. Case report and literature review of auto-brewery syndrome: probably an underdiagnosed medical condition. BMJ Open Gastroenterol. 2019;6(1): e000325.

11 Cederbaum AI. Alcohol metabolism. Clin Liver Dis. 2012;16(4):667– 685.

12 Patel S, Behara R, Swanson GR, Forsyth CB, Voigt RM, Keshavarzian A. Alcohol and the intestine. Biomolecules. 2015;5(4):2573–2588.

13 Baraona E, Julkunen R, Tannenbaum L, Lieber CS. Role of intestinal bacterial overgrowth in ethanol production and metabolism in rats. Gastroenterology. 1986;90(1):103–110.

14 Turnbaugh PJ, Hamady M, Yatsunenko T, et al. A core gut microbiome in obese and lean twins. Nature. 2009;457:480–484.

15 Lepage P, Hasler R, Spehlmann ME, et al. Twin study indicates loss of interaction between microbiota and mucosa of patients with ulcerative colitis. Gastroenterology. 2011;141:227–236.

16 Qin J, Li Y, Cai Z, et al. A metagenome-wide association study of gut microbiota in type 2 diabetes. Nature. 2012;490:55–60.

17 Natividad JM, Agus A, Planchais J, et al. Impaired aryl hydrocarbon receptor ligand production by the gut microbiota is a key factor in metabolic syndrome. Cell Metab. 2018;28:737–749.e4.

18 Yuan J, Chen C, Cui J, et al. Fatty liver disease caused by highalcohol- producing Klebsiella pneumoniae. Cell Metab. 2019;30:675–688.e7.

19 Bayoumy AB, Mulder CJJ, Mol JJ, Tushuizen ME. Gut fermentation syndrome: a systematic review of case reports. United European Gastroenterol J. 2021;9(3):332–342.

20 Dinis-Oliveira RJ. The auto-brewery syndrome: a perfect metabolic “storm” with clinical and forensic implications. J Clin Med. 2021;10(20):4637.

21. Khaderi SA. Introduction: Alcohol and Alcoholism. Clin Liver Dis. 2019;23(1):1–10.

22. Amr S, Tbakhi A. Abu Bakr Muhammad Ibn Zakariya Al Razi (Rhazes): philosopher, physician and alchemist. Ann Saudi Med. 2007;27(4):305–7.

23. The global burden of disease attributable to alcohol and drug use in 195 countries and territories, 1990-2016: a systematic analysis for the Global Burden of Disease Study 2016. Lancet Psychiatr. 2018;5(12):987-1012.

24. Painter K, Cordell BJ, Sticco KL. Auto-Brewery Syndrome (Gut Fermentation). StatPearls Publishing LLC; 2020.

25. Malik F, Wickremesinghe P, Saverimuttu J. Case report and literature review of auto-brewery syndrome: probably an underdiagnosed medical condition. BMJ Open Gastroenterol. 2019;6(1): e000325.

26. Bivin WS, Heinen BN. Production of ethanol from infant food formulas by common yeasts. J Appl Bacteriol. 1985;58(4):355–7.

27. Yuan J, Chen C, Cui J, Lu J, Yan C, Wei X, et al. Fatty liver disease caused by high-alcohol-producing *Klebsiella pneumoniae*. Cell Metabol. 2019;30(4):675–88.

28. Dawes EA, Foster SM. The formation of ethanol in Escherichia coli. Biochim Biophys Acta. 1956;22(2):253–65.

29. Mitchell MC, Teigen EL, Ramchandani VA: Absorption and peak blood alcohol concentration after drinking beer, wine, or spirits. Alcohol Clin Exp Res. 2014, 38:1200-4. 10.1111/acer.12355

30. Gentry RT: Effect of food on the pharmacokinetics of alcohol absorption . Alcohol Clin Exp Res. 2000, 24:403-4. 10.1111/j.1530-0277.2000.tb01996.x

31. Logan BK, Jones AW: Endogenous ethanol 'auto-brewery syndrome' as a drunk-driving defence challenge . Med Sci Law. 2000, 40:206-15. 10.1177/002580240004000304

32. Akbaba M. A medicolegal approach to the very rare auto-brewery (endogenous alcohol fermentation) syndrome. Traffic Inj Prev. 2020;21(5):295–7.

33. Chen AI, Dolben EF, Okegbe C, et al. *Candida albicans* ethanol stimulates *Pseudomonas aeruginosa* WspR-controlled biofilm formation as part of a cyclic relationship involving phenazines. PLoS Pathog. 2014;10(10):e1004480.

34. Painter K, Cordell BJ, Sticco KL. *StatPearls [Internet]* Treasure Island, FL: StatPearls Publishing; 2020. Auto-brewery syndrome (gut fermentation) [Google Scholar]

35. Gut microbiome and antibiotics. Iizumi T, Battaglia T, Ruiz V, Perez Perez GI. *Arch Med Res*. 2017;48:727–734. [PubMed] [Google Scholar]

36. Auto-brewery syndrome: ethanol pseudo-toxicity in diabetic and hepatic patients. Hafez EM, Hamad MA, Fouad M, Abdel-Lateff A. *Hum Exp Toxicol*. 2017;36:445–450. [PubMed] [Google Scholar]

37. Auto-brewery syndrome in the setting of long-standing Crohn's disease: a case report and review of the literature. Welch BT, Prabhu NC, Walkoff L, Trenkner SW. *J Crohns Colitis.* 2016;10:1448–1450. [PubMed] [Google Scholar]

38. Auto-brewery syndrome in a child with short gut syndrome: case report and review of the literature. Dahshan A, Donovan K. *J Pediatr Gastroenterol Nutr.* 2001;33:214–215. [PubMed] [Google Scholar]

39. Endogenous ethanol fermentation in a child with short bowel syndrome. Jansson-Nettelbladt E, Meurling S, Petrini B, Sjolin J. *Acta Paediatr.* 2006;95:502–504. [PubMed] [Google Scholar]

40. Endogenous ethanol production in a patient with chronic intestinal pseudo-obstruction and small intestinal bacterial overgrowth. Spinucci G, Guidetti M, Lanzoni E, Pironi L. *Eur J Gastroenterol Hepatol.* 2006;18:799–802. [PubMed] [Google Scholar]

41. Endogenous ethanol 'auto-brewery syndrome' as a drunk-driving defence challenge. Logan BK, Jones AW. *Med Sci Law.* 2000;40:206–215. [PubMed] [Google Scholar]

42. Sulforaphane accelerates acetaldehyde metabolism by inducing aldehyde dehydrogenases: relevance to ethanol intolerance. Ushida Y, Talalay P. *Alcohol Alcohol.* 2013;48:526–534. [PubMed] [Google Scholar]

43. Vandekerckhove E, Janssens F, Tate D, De Looze D. Treatment of Gut Fermentation Syndrome With Fecal Microbiota Transplantation. Ann Intern Med. 2020 Nov 17;173(10):855. [PubMed] [Reference list]