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Effect of Auto Brewery Syndrome in general and Oral Health Systematic Review and Meta analysis

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Abstract

Introduction: The gut fermentation syndrome (GFS), also known as the endogenous alcohol fermentation syndrome or auto brewery syndrome, is a rare and under- diagnosed medical condition where consumed carbohydrates are converted to alcohol by the microbiota in the gastrointestinal or urinary tract. The symptoms of GFS can have severe impact on patients' wellbeing and can have social and legal consequences. Unfortunately, not much is reported about GFS. The aim of this systematic review was to assess the evidence for GFS, causal micro-organisms, di- agnostics, and possible treatments.

Material and Methods: A protocol was developed prior to initiation of the systematic review (PROSPERO 207182). We performed a literature search for clinical studies on 1 September 2020 using PubMed and Embase. We included all clinical studies, including case reports that described the GFS.

Results: In total, 17 case reports were included, consisting of 20 patients diagnosed with GFS. The species that caused the GFS included Klebsiellapneumoniae, Candida albicans, C. glabrata, Saccharomyces cerevisiae, C. intermedia, C. parapsilosis, and C. kefyr.

Conclusions: GFS is a rare but underdiagnosed disease in daily practice. The disease is mostly reported by Saccharomyces and Candida genera, and some cases were previously treated with

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antibiotics. Studies in Nonalcoholic Fatty Liver disease suggest a bacterial origin of endogenous alcohol-production, which might also be causal micro-organisms in GFS. Current treatments for GFS include antibiotics, antifungal medication, low carbohydrate diet, and probiotics. There might be a potential role of fecal microbiota transplant in the treatment of GFS.

Keywords: Auto-Brewery Syndrome, Drunkenness Disease, Endogenous Alochol Fermentation Syndrome.

Introduction

The consumption of alcoholic beverages is as old as human history and dates back to early civilizations such as ancient Egypt and ancient China.1 The distillation of alcohol (الكحل, al-Kuhl) can be attributed to early scientists from the Islamic world.2 Ethanol- containing alcoholic beverages are one of the most widely used and accepted recreational drugs worldwide.3 Excessive consumption of alcoholic beverages has negative medical and social consequences. However, some individuals might suffer from these consequences without consuming any alcohol. These unfortunate individuals suffer from the so-called gut fermentation syndrome (GFS), also known as the endogenous alcohol fermentation syndrome, gut fermentation syndrome, or auto-brewery syndrome.4 We suggest to referthis disease as gut-fermentation syndrome in future literature. GFS is a rare and underrecognized medical condition. Consumed carbohy- drates are metabolized to alcohol by fungi and/or bacteria in the gastrointestinal tract.5 Fungi are not commonly present in the upper gastrointestinal tract, but may be present in the colon as part of the commensal microbiome. There are some fungi that are known that produces ethanol such as fungi from the *Candida* and *Saccharomyces* genera.6 Recently, also the role of bacteria including *Klebsiella*and *Escherichia* in intestinal alcohol production have becomeapparent.7,8 The pathological colonization of alcohol-producing fungi and bacteria in the gastrointestinal, but also the urinary tract, can lead to overproduction of endogenous alcohol and may lead to symptoms of GFS in exceptional cases. Symptoms include decreased social inhibition, decreased peripheral vision, ataxia, nausea, and slurred speech, similar to those of excessive alcoholic consumption. These symptoms can have severe impact on patients' wellbeing and can have social and legal consequences. Unfortunately, not much is known about GFS, and its existence is not known to manyphysicians. Therefore, the aim of this systematic review was to assess the evidenceforGFS,includingdiagnosticsandtreatmentoptions.

Material and methods

We systematic searched PubMed and Embase from inception up to September 2020 for any clinical evidence for GFS. This electronic search strategy was augmented by a manual examination of refer- ences cited in articles, recent reviews, editorials, and meta-analyses. No restrictions were imposed on the language, study period, or sample size.Two investigators (AB and CJM) independently screened titles and abstracts, identified duplicates, reviewed full articles, and determined their eligibility. Any discrepancies were resolved by reaching a consensus regarding the inclusion or exclusion of a trial between the two researchers.The data compiled a standardized form to extract the following study characteristics: study design, number of patients, age, BMI, previous antibiotic treatment, symptoms, differential diagnosis, micro- organism, and all given treatments.

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Results

From a total of 821 articles, 17 case reports involving 20 patients were finalized. **Figures 1** A summary of the risk of bias assessment is provided in **Table 1**. All studies were case reports. Seven studies13–18 were judged as good, seven studies19–24 were judged as fair and two studies25,26 were poor in terms of risk of bias.The patients described in the included case reports had various initial symptoms at presentation.

FIGURE 1: FLOW CHART DESCRIBING THE SELECTION OF THE STUDIES

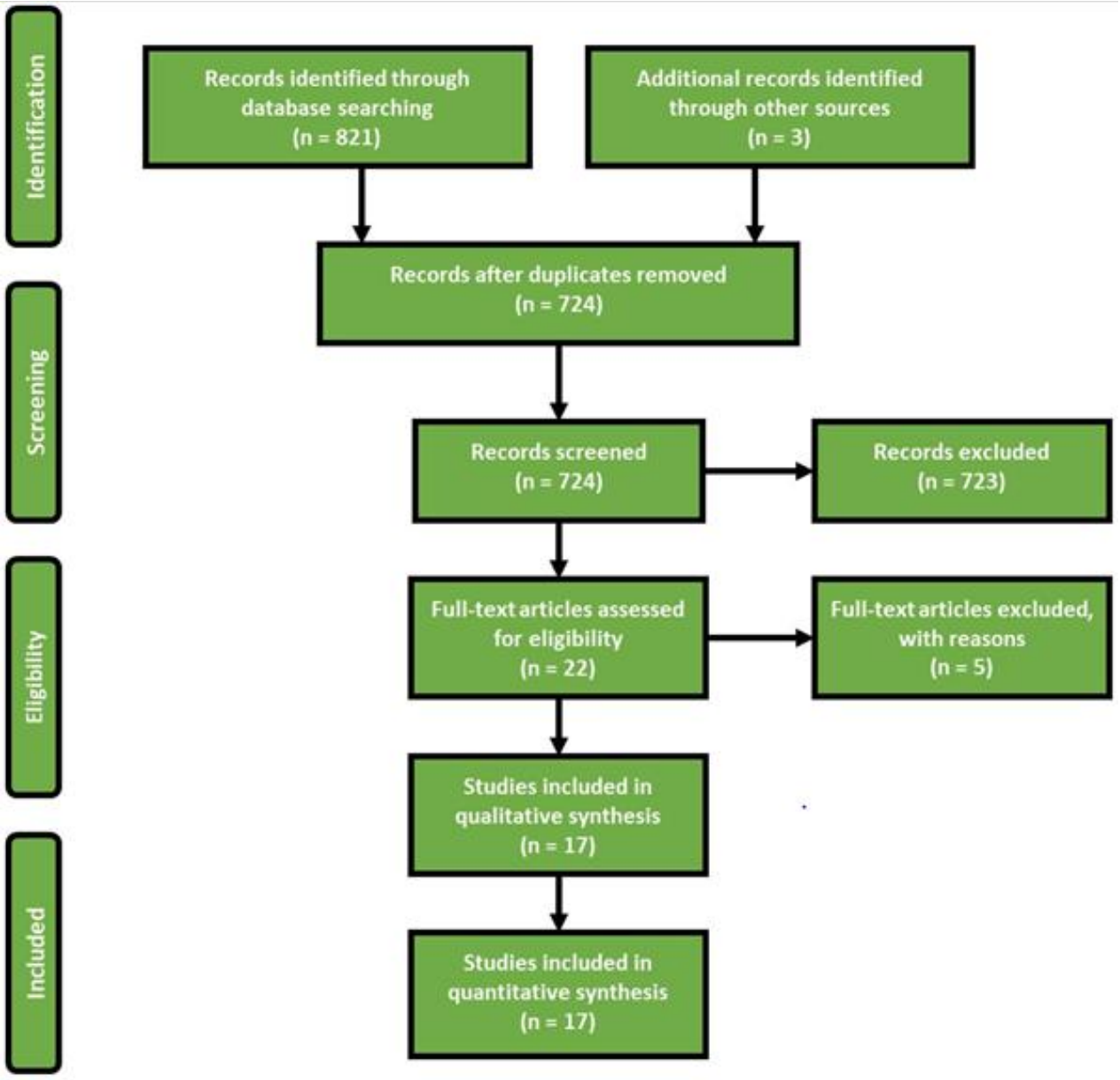

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TABLE 1 SUMMARY OF STUDIES AND RISK OF BIAS ANALYSIS

Author	Design	Country	Year	Setting	Risk of bias judgment
Vandekerckhove[13]	CR	Belgium	2020	Hospital	Good
Kruckenberg[14]	CR	USA	2020	Hospital	Good
Akbaba[15]	CR	Turkey	2020	Hospital	Good
Yuan[7]	CR	China	2019	Hospital	Poor
Saverimuttu[16]	CR	USA	2019	Hospital	Good
Malik[5]	CR	UK	2019	Hospital	Good
Akhavan[19]	CR	USA	2019	Hospital	Fair
Ahmed[20]	CR	USA	2018	Hospital	Fair
Guo[21]	CR	China	2018	Hospital	Fair
Mishra[22]	CR	USA	2017	Hospital	Fair
Welch[23]	CR	USA	2016	Hospital	Fair
Cordell[25]	CR	USA	2015	Hospital	Poor
Cordell[24]	CR	USA	2013	Hospital	Fair
Jansson□Nettelbladt[27]	CR	Sweden	2006	Hospital	Fair
Spinucci[17]	CR	Italy	2006	Hospital	Good
Dahshan[18]	CR	USA	2001	Hospital	Good
Kaji[26]	CR	Japan	1984	Hospital	Poor

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TABLE 2: COMPARISON OF THE STUDIES

Author	Age	Sex	BMI	Symptoms	First differential diagnosis	Comorbidity	AB use?	alcohol Consumption?	Micro□organisms	Blood level of ethanol	Treatment	of symptoms ?
Yuan[7]	NA	NA	NA	NA	NASH	NA	NA	Yes	*Klebsiella pneumoniae*	400 mg/L	Antifungal treatment ineffective. Antibiotics and diet more effective	NA
Vandekerckhove[13]	47	M	NA	Intermittent episodes of drunkenness + ↑LFT	GFS	RY bypass	Yes	Yes	*Candida glabrata*	34.7 mmol/L	Fluconazole 100 mg + low carb diet, nystatin, 500, 000 IU, amphotericin B 100 mg, FMTOral fungal treatment	Yes
Kruckenberg[14]	61	F	NA	Screening	Hidden alcohol use	DM II, cirrhosis	No	No	*C. glabrata* *S. cerevisiae* (urinary)	18 mg/dl		No
Akbaba[15]	38	M	NA	Car accident while drunk	Alcohol abuse	HT, alcohol abuses, sleep disorder	No	No	*Pseudomonas*	257.8 mg/dl	NA	NA
Saverimuttu[16]	45	M	35	Recurrent seizures	Alcohol abuse	DM II	Yes	No	*S. cerevisiae* *C. intermedia*	410 mg/dl	Fluconazole 100 mg + probiotica Intravenous micafungin	Yes
Malik[5]	46	M	30	Memory loss, mental changes and episodes of depression	GFS	None	Yes	No	*Saccharomyces* and *C.* fungi	57 mg/dl	Fluconazole 150 mg, itraconazole 150 mg, micafungin 150 mg	Yes
Akhavan[19]	25	M	NA	Slurred speech, fatigue, stumbling, dizziness and nausea	Celiac disease, thyroid disease	None	No	Yes	NA	30 mg/dl	Fluconazole 100 mg	Yes
Ahmed[20]	45	M	NA	Vomiting, edema, slurred speech, hallucinations and loss of consciousness, precipitated after meals.	GFS	Obese, DMII	Yes	Yes	*S. cerevisiae* *C. intermedia*	NA	Fluconazole + low carbohydrate diet	Yes
Guo[21]	30	M	NA	Recurrent unexplained GI discomfort, intoxication, ↑LFT	Alcohol abuse	None	No	Yes	*C. parapsilosis*	311.2 mg/dl	Fluconazole 150 mg + Bifico, voriconazole 400 mg, nystatin 200 MU	Yes
Mishra[22]	45	M	NA	↑ alcohol in traffic test	GFS	DMII, obese	No	Yes	Not found	NA	Fluconazole	Yes
Welch[23]	71	M	NA	Slurred speech and walking difficulties.	GFS	IBD(CD)	Yes	Yes	*C. glabrata*	170 mg/dl	Low carbohydrate diet	Yes
Cordell[25]	60	M	33	1. Episodes of drunkenness,	1. Alcohol abuse2.	HepC, HT	No	Yes	1. *C. albicans*, *C. krusei*	170	1. Low carbohydrate diet	Yes
	42	F	NA	depression	Alcohol abuse3.	None	No	Yes	2. *S. cerevesiae*,	mg/dl	2. Fluconazole + low	Yes
	32	M	22	2. Episodes of drunkenness 3. Intoxication	Alcohol abuse	None		Yes	*S. bulardii* 3. *S. cerevesiae*	NA NA	carbohydrate diet. 3. Fluconazole 150 mg, nystatin, low carbohydrate diet	No
Cordell[24]	61	M	NA	Intoxications	Hidden alcohol use	HT	Yes	No	*S. cerevisiae*	120 mg/dl	Fluconazole 100 mg + nystatin 500, 000 IU	Yes
Jansson□ Nettelbladt[27]	3	F	NA	Fruity breath odor and walking difficulties	GFS	Small bowel malformation	No	No	*C. kefyr* *S. cerevisiae*	15 mmol/L	Fluconazole 100 mg + low carbohydrate diet	Yes
Spinucci[17]	44	M	16	Mental confusion, disorientation and slurred speech.	Alcohol abuse	Chronic intestinal Pseudo□ obstruction	Yes	No	*C. albicans* *S. cerevisiae*	24.9 mg/dl	Fluconazole 100 mg + low carbohydrate diet	Yes
Dahshan[18]	13	F	NA	Bizarre behavior, somnolence, disorientation and fruity breath odor	Alcohol abuse	Short bowel syndrome	No	No	*C. glabrata S. cerevisiae*	250□350 mg/dl	Fluconazole 100 mg	Yes
Kaji[26]	24	FM	NA	1. Seizures, nausea and vomiting.2. Fruity breath odor, slurred speech, blurred vision and walking difficulties	1. GFS	None	No	Yes	*C. albicans*	254	Low carbohydrate diet.	Yes
	35				2. FS	None	No	Yes		mg/dl	Nystatin, metronidazole	

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These symptoms include: slurred speech17,19,20,23,26 (n = 5), fruity breath odor18,26,27 (n = 3), walking difficulties19,23,26,27 (n = 5), episodes of depression5,25 (n = 2), seizures16,26 (n = 2), vomiting19–21,26 (n = 4), intoxicated feeling5,13,17,18,21,24,25 (n = 7), and disorientation17–19 (n = 3). The median age of patients was 44 years old (range: 3–71) and 14 patients were male (70%).Eighteen out of 20 case reports described various micro-organisms that caused the GFS. The species included K. pneumoniae, C. albicans, C. glabrata, S. cerevisiae, C. intermedia, C. parapsilosis, and C. kefyr. One study mentioned they found Pseudomonas bacteria in a duodenal aspirate.15 Pseudomonas is rarely present in the micro-biome; however, the coinfection of Pseudomonas and C. genera is relatively common. P. aeruginosa biofilm formation and phenazine production is strongly influenced by ethanol production by C. albicans.33 However, in the case described by Akbabaet al.15 no fungal organisms were found in the fungal culture. The diagnosis GFS was made after the carbohydrate challenge test was positive, without identifying a causal micro-organism.Patients used antibiotics shortly before the onset of symptoms in seven case reports.5,13,16,17,20,23,24The complete evaluation of the GFS includes history taking, physical examination, laboratory testing, stool sampling with culture, a carbohydrate challenge test, and endoscopy with biopsies for culture. In five case reports, fluconazole 100 mg/day for 3 weeks and/or low- carbohydrate diet was sufficient to treat the GFS.16,18,19,23,27 These other treat- ments included nystatin, amphotericin, micafungin, itraconazole, voriconazole, metronidazole, or combinations thereof. **Table 2.**

Discussion

The cases showed that GFS often is misdiagnosed and that it comes along with somatic and social suffering. Most patients were suspected for alcohol abuse even though patients denied using alcohol, which is a typical presentation for this disease. All patients were either treated with antifungal therapy and/or low carbohydrate diet. One patient was ultimately treated with FMT.13 GFS is generally well-treatable if the syndrome is recognized by physicians.Five case reports5,13,16,17,23 described recent antibiotics use before or at onset of symptoms. The use of antibiotics might affect the micro- biome, and would allow for colonization of alcohol-producing species. The micro-organisms that are described in this study were usually from the Saccharomyces and Candida genera. K. pneumoniae was also found in gastric and jejunal samples in the case presented by Saverimuttuet al.16 However, in their case, K. pneumoniae was still present in the microbiome after successful treatment of Candida intermedia with micafungin. Symptoms did not reoccur after treatment. Other potential microbial genera that are capable of producing endogenous ethanol are Escherichia,8 Streptococcus,40 Bacteroides,41 Bifidobacte-rium,42 and Clostridium.43 Identification of these micro-organisms in patients suspected of GFS might perhaps be the causal organisms, which needs adequate therapy. However, till so far no such cases have been published. Unfortunately, no case control studies have been performed for GFS. As GFS is a rare disease that is often misdiagnosed or unrecognized, a low amount of reports have been published. Physicians should be aware of this rare but unpleasant diagnosis. As shown in some of the case reports, patients were misdiagnosed as alcohol abusers.

Conclusion

GFS is a rare, and often a misunderstood and unrecognized condi- tion that physicians should consider or be aware of. The literature only consists out of case reports, no high level evidence studies have been performed regarding prevalence and treatment. The disease is mostly caused by Saccharomyces and Candida genera, and some cases were previously treated with antibiotics.

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In a few case reports, risk factors such as diabetes mellitus, liver cirrhosis, and prior intestinal operations have been identified. Diagnosis can be made by adequate history taking and carbohydrate challenge test. Current treatments include antifungal medication, low carbohydrate diet, and probiotics. There might be a future role of FMT in the treatment of GFS. Low-grade GFS should be considered and studied in NASH as well

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