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AN INTOXICATED TEETOTALER: A CLINICAL IRONY

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ABSTRACT

Auto brewery syndrome is a rare condition characterized by endogenous production of ethyl alcohol by gut microflora with clinical symptoms mimicking those of alcohol intoxication. Its associated medicolegal impacts warrants an accurate diagnosis with adequate history recording, culture testing and a confirmatory glucose challenge test. However, its non-specific symptoms renders its diagnosis and management to be daunting task thus highlighting the need of further research. This review article is an attempt to summarize the available literature aiding in better comprehension of this disorder.

INTRODUCTION

Alcohol intoxication has been a part of our social life in varying proportions across the globe.[1]It is also subjected to numerous medicolegal implications due to its neurological and psychiatric effects thus making blood ethyl alcohol level testing an imperative tool for its detection.[2] Therefore, the emergence of concepts indicating endogenous production of ethyl alcohol by the body instead of external consumption has both been assuming and menacing.[3] The idea of being drunk without drinking carries with it magnanimous medicolegal and health hazard which needs to be resolved with an urgent commitment. Since alcohol undergoes first pass metabolism before entering the blood stream and being detected, its endogenous production in such large quantities is still unsubstantiated though its pharmacokinetics can be influenced by many variables.[4,5,6] Thus, this review article aims to compile and spread awareness about Auto Brewery syndrome/ gut fermentation syndrome which is a rare or an under diagnosed condition wherein ethanol is produced by carbohydrate fermentation by gut fungi/bacteria producing all symptoms similar to alcohol intoxication.[7]

PREDISPOSING FACTORS

Though it can affect healthy individuals ,however those consuming high carbohydrates/sugar diet and refined foods and those with existing gut problems and debilitating diseases like obesity, Crohn disease, diabetes mellitus type II and liver cirrhosis are found to be more prone.[3,8,9,0,11] Along with these, the overuse of antibiotics disturbing the gut microflora has also been associated with higher risk of development of Auto Brewery syndrome.[12] Recently a correlation between use of antacids like cimetidine with increased ethanol production in the gastric juice has been discovered by Bode et al. wherein it has been claimed that due to a change in pH caused by these antacids they result in increased proliferation of gut microflora in turn leading to more ethanol production.[13]

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ETIOLOGY

Yeasts such as *Saccharomyces cerevisiae, S. boulardii,, Candidda glabrata, C. albicans, C. kefyr,* and *C. parapsilosis* have been identified as causes of this condition. [8-11,14-20]The validation of their involvement in the production of ethanol was done by Bivin and Heinen .*Candida albicans*, *Candida tropicalis*, *Saccharomyces cerevisiae*, and *Torulopsis glabrata* were combined and tested for ethanol production by gas chromatography after 24 and 48 hours substantiating ethanol production by patients exhibiting auto-brewery syndrome.[21]

The bacteria *Klebsiella pneumonia* and *Enterococcus faecium* have also been implicated in rare conditions.[15] They attributed to production of EnEth leading to development of non-alcoholic fatty liver disease. Higher levels of EnEth were detected in obese patients and those with non-alcoholic steatohepatitis.[2] Baraona et al. demonstrated ethanol formation by bacteria residing in the intestine in rats.[22]

EPIDEMIOLOGY

Gut fermentation syndrome has been found to equally affect all age groups and males and females as well. Al-Awadhi et al. in their study in the United Arab Emirates demonstrated equal levels of endogenous ethanol production irrespective of age, gender and nationalities.[23] These results were further substantiated by Ragab et al. on the Saudi Arabia population.[24]On the other hand, Nair et al. in their study involving non-alcoholic steatohepatitis patients found higher levels of breath alcohol in obese and females.[25] A significant study by Cordell et al concluded considerable lifestyle differences between healthy individuals and those with ABS syndrome. Overall, patients with ABS syndrome were found to be less healthy with frequent bowel movements, oral malodour and more food allergies. They were found to consume more water, less hot beverages and preferred eating at home with more aversion to starch.[7]

PATHOPHYSIOLOGY

Though some amount of endogenous alcohol production has been considered normal, a typical perturbation of the gut microflora has been identified as a prerequisite for over colonizing of these fermenting microbes. Ethanol concentration as high as 400 mg/dL has also been identified owing to consumption of high carbohydrate diet with stress, skipping meals and antibiotics exacerbating the condition.[7,12]

It's found to be frequently associated with other co morbidities as concluded by Hafez et al. who found significantly higher levels of blood ethanol in those with diabetes mellitus type 2 (4.85 ± 3.96 mg/dL) and liver cirrhosis (3.45 ± 2.65 mg/dL) as compared to the control group(0.3 ± 0.41 mg/dL).[26] Such high levels of ethanol were also demonstrated in patients exhibiting conditions like Crohn's disease, short bowel syndrome, and chronic intestinal pseudo-obstruction.[8-11] Though variation in dietary intake and genetic polymorphism of aldehyde dehydrogenase enzyme responsible for hepatic and first pass metabolism of alcohol is an important contributory factor which needs to be explored further.[3,6,27]

CLINICAL PRESENTATION

Patients with gut fermentation syndrome typically present with all signs of alcohol intoxication which can broadly be categorized as neurological, gastrointestinal, psychological and respiratory problems. Neurological symptoms can include lack of coordination, slurred speech, blurred vision, seizures, fainting and dementia.[14-16] Gastrointestinal problems include generalized abdominal discomfort, blenching, vomiting, diarrhoea, nausea leading to irritable

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bowel symptoms.[17,20] The psychological symptoms include bizarre behaviour, disorientation, somnolence, confusion and a state of chronic fatigue. This state of fatigue can result in anxiety, depression and overall poor productivity of an individual.Though respirator symptoms such as rhinitis and cough have also been reported however their incidence has been found to be relatively low.[9,28]

Apart from these, its strain on social relationships and the danger of meeting a fall or an accident while driving due to high blood ethanol level and its associated medicolegal aspects cannot be ignored. Thus, due to wide range of non-specificity of symptoms, its diagnosis and differential from other aetiologies is of utmost significance.[3]

DIFFERENTIAL DIAGNOSIS

ABS must be differentiated with other conditions presenting similar clinical outcomes like head trauma, closet drinking, lactic acidosis, and other psychiatric disorders.[3,29] This condition must be considered in differential diagnosis of patients exhibiting signs and symptoms of alcohol intoxication with no history of alcohol consumption particularly consuming a high carbohydrate diet or presenting with other predisposing factors.

DIAGNOSIS

Firstly, a complete medical, drug, habit and diet history including history from family members regarding alcohol and diet intake for verification should be recorded. Secondly, laboratory tests like complete blood count, blood alcohol level, metabolic panel, drug screen and faeces culture and sensitivity. This must be followed by elimination of any other primary causes of differential diagnosis. Following which the confirmatory test for ABS that is glucose challenge test must be carried out.. Traditionally, there are two types of such tests available, the nonspecific one involves provision of a carbohydrate meal and subsequent detection of alcohol in breath and blood.[14] Whereas, a standardized test involves administration of a specific amount of glucose and then detection of endogenous ethanol production. Varying protocols of such glucose administration has been proposed till date with Hunnisett et al. being the first one. His method involved administering 50 g oral glucose to the first group after overnight fasting whereas the group suspected of ABS was given 5g glucose. Alcohol refrain from last 24 hours and no food consumption from at least last three hours was ensured. BAL of 0.5mg/dl was set to be a positive value in accordance with which both groups showed increased values (69% and 61%, respectively) of blood ethyl alcohol after an hour indicting gut fermentation.[30] Eaton then modified the procedure and administered 1g glucose as a hard gelatin capsule to both the groups followed by 4g glucose. He conclusively showed an increase of BAL from 1-7 mg/dl only in the suspected group while no increase was noted in the control group.[28]

Finally the most adopted test was introduced by Malik et al. wherein carbohydrate challenge of 200 g glucose with BAC and BrAC is done at 0,1/2,1,2,4,8,16 and 24 hours interval. This huge time interval of 24 hours has been added considering that few gut fungi can take up to this time to ferment.[14] This diagnostic test can be coupled with upper and lower endoscopy to obtain samples for culture and sensitivity.

MANAGEMENT

A well-coordinated multidisciplinary team with patient compliance being central is of utmost requirement. Foremost is the stabilization of patient in case of extreme intoxication by means

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of maintaining airway, breathing and fluid administration.[3,31] Subsequent management by appropriate drug therapy based on culture and sensitivity. Mostly, a course of mono or in some instances poly azoles or polyenes have found to be effective. Some commonly used antifungals include fluconazole, nystatin, micafungin, trichomycin B, and voriconazole.[9-11,14-17]While few cases of bacteria or resistant microbes require antibiotics or echinocardin. While diet modification and lifestyle change forms the pivotal part of therapy with replacement of carbohydrates and sugars with a protein rich diet thus depriving the gut microbes of their substrate to produce any more ethyl alcohol.[3] Additionally, balancing the gut microbial flora with the aid of multistrain probiotic supplements or Lactobacillus may be advised though its beneficial effects are still not substantiated.[15] However, a special care of not creating any imbalance between the beneficial and harmful microbes of the gut by in advent use of antibiotics etc must be avoided. Adoption of all the above combinations for lifetime are essential for maintaining a healthy state and prevent relapse of auto Brewery syndrome. Along with this a complete abstain from alcohol consumption is advised.[3]

PROGNOSIS

Though most patients can sustain with just diet modification and adoption of precautions like alcohol and antibiotics refrain, few might need continuation of antifungals or antibiotics with frequent testing of any resistance or new sensitivity development.[2,3]

COMPLICATIONS

Though most of the patients can resume a normal lifestyle following treatment, few can encounter a relapse due to extreme perturbation of gut microflora. The associated legal and social hazards caused due to symptoms similar to alcohol intoxication also needs to be dealt with. In rare conditions long term retention of endogenous alcohol can develop a craving and subsequent addiction for external alcohol consumption making it a viscous chain.[3]

Few studies by Zhu et al. even advocated development of NASH by the same fermenting microbes posing a great health hazard.[32] Eaton et al. has advocated these gut microbes to deteriorate body vitamins and minerals thus imposing respective deficiency symptoms. Vitamin B6 was found to highly depleted along with zinc and Magnesium being the most affected minerals.[31] In rare instances ABS has also been associated with infant death syndrome though more research regarding the same is still required.[34]

MEDICO-LEGAL ASPECT

ABS has gained a highly controversial position in the field of forensic medicine with admissible values of BAL and breath alcohol being repeatedly challenged in the courts on one hand and in the other external consumption of alcohol being denied on grounds of existence of ABS syndrome. Thus, multiple studies have been carried out to demonstrate the possible level of endogenous ethyl alcohol production with varying results and with many influencing factors. The detection has been carried out in different body fluids including blood, urine, breath and plasma utilizing enzymatic oxidation and gas chromatography.Most of them confirmed the production of small amount of endogenous alcohol production by the body although level as high as 80mg/dl were found to be rare associated with ABS syndrome.[2,6] Many influencing factors have also been deduced like Simic et al. concluded that patients with Diabetes mellitus had higher BAL (2.65 mg/dL vs 0.40 mg/dL) and urine alcohol levels (6.13 mg/dL vs 3.27 mg/dL) compared to healthy counterparts using the

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headspace gas chromatography method. However by using the Widmark's method even higher values of BAL were seen for the diabetic group (27.28 mg/dL), though it was still lower than the level for illegal intoxication and even urine alcohol levels were found to be much higher (54.27 mg/dL vs 8.30 mg/dL).[35]On the contrary, Alexander et al. in their study compared the urine alcohol levels of ten diabetic patients with healthy counterparts and concluded that even though the initial levels detected by gas chromatography were minimal however following three weeks a substantial rise in urine alcohol level was detected (700 mg/dL).[36] Thus, this huge variability in the literature warrants more research to be directed to have conclusive results.

CONCLUSION

Thus, not every patient presenting with symptoms of alcohol intoxication should be treated with suspicion instead they may require more empathy and compassion. An integrated multi-disciplinary approach involving a gastroenterologist, an infectious disease specialist, a nutritionist, a pharmacist, a nurse and a primary provider must be framed. Since ABS is a rare syndrome therefore a wider spectrum of knowledge and comprehension of its non-specific symptoms with adequate history taking must be performed to avoid unnecessary legal hazards it may cause.[2,3]

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