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Case Report

The case study of one patient with gut fermentation Syndrome: case report and review of the literature

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Abstract: Gut Fermentation Syndrome, also known as Auto-Brewery Syndrome, is rarely encountered in clinical practice. It was first described in 1952 in Japan, after that, only very few cases have been reported from Japan and several western countries, here we reviewed and report a male patient, who was 30 years old, with progressively digestive tract and intoxication symptoms as well as abnormal liver functions. The blood alcohol concentration of this patient elevated without ethanol intake, and the detection results of stool cultures indicated the causative organism was Candida parasilosis (Figure 1). Finally, the symptoms of patient received antifungal agent therapy. The purpose of this article is to describe the clinical manifestation of the rare syndrome, review the relative literatures, and improve clinicians' understanding of diagnosis and treatment of Gut Fermentation Syndrome.

Keywords: Gut fermentation syndrome, digestive tract symptoms, intoxication, abnormal liver functions, antifungal

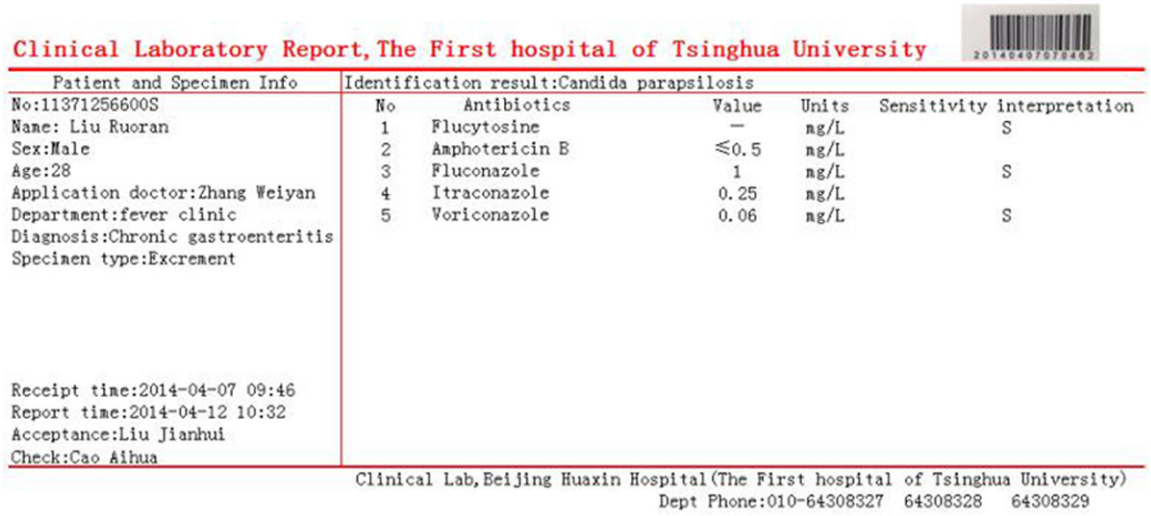
Introduction

Gut Fermentation Syndrome is described as a syndrome whereby patients become intoxicated without ingesting alcohol, which usually occurs after a heavy carbohydrate meal or a period of time of using antibiotics. Moreover, an overgrowth of intestinal flora (bacteria or fungi) has often been found among these patients. The underlying mechanism is the endogenous ethanol production results from fermenting carbohydrate induced by flora, which elevated blood alcohol concentrations (BACs). In most cases, decreased carbohydrate intake alone or combination with antifungal agent therapy and limit abuse of antibiotics can subside the symptoms. Several terms such as intestinal carbohydrate dyspepsia, Auto-Brewery Syndrome, and endogenous ethanol fermentation had been used to describe this condition before Gut Fermentation Syndrome has been formally named since 1990 [1].

Review of literature

The first case was described in 1948 [1], who was a 5-year-old Acholi boy died due to rupture of the stomach caused by marked distension of the gastrointestinal tract. The necroscopy findings revealed the presence of gas and liquid that smelled like ethyl alcohol in the stomach and peritoneum. The author hypothesized that alcohol had been produced by the fermentation of sweet potatoes induced by the intestinal bacteria (Gram-negative cocci and bacilli) in the gastric and peritoneal juices. Unfortunately, the blood ethanol concentration wasn't detected at that time.

In 1952, Sato [2] described a 46-year-old male patient with pylorostenosis who became intoxicated after exploratory laparotomy. The causative organism was Candida determined by bacterial cultures (**Figure 1**), and this case was considered the earliest formal report for this syndrome. Moreover, Iwata [3] detailed 12 cases prior to 1972. In 1984, Kaji [4] *et al* reported two cases and reviewed a Japanese population of 37 patients with gastrointestinal alcohol fermentation caused by yeast. Few adult cases of Gut Fermentation Syndrome have been described from other countries in the past decade. In 2006, an Italian literature [5] reported a 44-year-old Caucasian man



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Patient and Specimen Info	Identification result:Candida parapsilosis
No:113712566005	
Name: Liu Ruoran	
Sex:Male	
Age:28	
Application doctor:Zhang Weiyan	
Department:fever clinic	
Diagnosis:Chronic gastroenteritis	
Specimen type:Excrement	
Receipt time:2014-04-07 09:46	
Report time:2014-04-12 10:32	
Acceptance:Liu Jianhui	
Check:Cao Aihua	

No	Antibiotics	Value	Units	Sensitivity interpretation
1	Flucytosine	—	ng/L	S
2	Amphotericin B	≤0.5	ng/L	
3	Fluconazole	1	ng/L	S
4	Itraconazole	0.25	ng/L	
5	Voriconazole	0.06	ng/L	S

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Figure 1. The causative organism was Candida determined by bacterial cultures, and this case was considered the earliest formal report for this syndrome.

receiving long-term home parenteral nutrition (HPN) for a chronic intestinal pseudo-obstruction, was hospitalized for belching and mental confusion. He had a history of oral antibiotic therapy with amoxicillin plus clavulanic acid for a small bowel bacterial overgrowth prior to symptoms onset. The laboratory findings showed the presence of ethanol in the blood, and gastric juice, furthermore, fecal microbiological cultures were positive for *C.albicans* and *S.cerevisiae*. His symptoms disappeared after antimycotic therapy with fluconazole. In 2013, Barbara [6] reported a 61-year-old American male with at least a five-year history of unexplained intoxication, and stool cultures demonstrated the causative organism was *Saccharomyces cerevisiae*. The patient also had a history of treatment with antibiotics and finally he was cured with antifungal agent therapy. Recently, Welch [7] described the case of a 71-year-old male with 50-year history of Crohn's disease who became intoxicated after ingesting foods high in sugar. He underwent external beam radiation and small bowel resection for rectum cancer about thirty years ago. Over the last three years, he received repeated courses of antimicrobial treatment for suspected small bowel bacterial overgrowth. High blood ethanol level was found during a symptomatic period without alcohol intake. CT demonstrated massive small bowel dilatation with anastomotic stricture, and a large amount of *Candida glabrate* grew from fluid collected from distended small bowel. Finally, he was no recurrent through changing his diet to a low carbohydrate diet and avoiding antibiotics.

This syndrome was also described in children. There were 3 children aged from 1 to 3 years in Kaji's cases [4], two of them with congenital stenosis of intestinal tract. Except Japan, similar instances of auto-brewery have been reported in three girls all with short bowel syndrome (SBS). Dahshan and Donovan [8] described a 13-year-old American girl with SBS secondary to resection for jejunal atresia and necrotizing enterocolitis. She had recurrent episodes of somnolence and a fruity odor on her breath for 6 months. The blood ethanol levels elevated repeatedly during the occurrence of symptoms, but she was with no access to alcoholic beverages. They noted that there were a strong correlation between high blood ethanol concentrations and the intake of high carbohydrate foods in this case. Aspirates from her small intestines fluids, then results of bacterial cultures indicated grew *Candida glabrata* and *Saccharomyces cerevisiae*. After fluconazole were given based on fungal sensitivity studies, the symptoms resolved and there was no recurrence of the elevated blood ethanol level. The other case [9] was a 3-year-old Swedish girl with a similar clinical manifestation. When she was started to receive enteral feeding gradually from total parenteral nutrition, the parents noticed the smell of alcohol in her bedroom and the bizarre behavior of the girl. Advanced dilated loops of

small bowel were showed by ultrasound and X-ray. Cultures from the gastric fluids and faeces demonstrated *Candida kefyr* and *Saccharomyces cerevisiae*. After, diets with low carbohydrate content and a course of flucinazole therapy, her symptoms eliminated. The third case [10] was a 12-year-old girl also from America. Before her episode, she had a history of urinary tract infection and treated with amoxicillin-clavulanic acid, then the patient began experiencing headache, dizziness, and confusion. *Candida glabrata*, *Enterobacter cloacae* and *Enterococcus faecium* were found in the culture of her small bowel aspirate. The treatment was changed to voriconazole according to drug sensitivity results.

Despite above cases have been reported, some scholars still questioned the existence of Gut Fermentation Syndrome. However, literature data have confirmed the generation of low levels of endogenous alcohol in healthy individuals, eg, a study [11] of 1557 residents in the United Arab Emirates showed that the pooled maximum blood alcohol level was 3.52 mg/dl (0.0035%) in males and 3.20 mg/dl (0.0032%) in females, which supported the production of endogenous ethanol, although it was too low to have any forensic significance.

Generally, the concentration of endogenous ethanol in blood is very low, sometimes on the verge of detectability by analytical methods. However, in certain conditions and metabolic disorders, endogenous ethanol levels can increase. Scientists found that overgrowth of some bacterial or yeast in gut can promote production of endogenous alcohol induced by fermentation of dietary carbohydrate.

What can cause the abnormal or unusual fermentation in the intestinal tract? As reported above, most cases showed various intestinal anatomy abnormalities and abnormal proliferation of the causative agent. Up to now, in six children cases, three with SBS, and two of them with congenital stenosis of intestinal tract. In a Japanese review [4], eighteen out of 36 adult cases were performed abdominal surgery. The organic or functional disturbance factors in gastrointestinal tract were quiet common, such as formation of blind loop, dilatation of small intestine, and reflux of duodenal content into the post-operative stomach. These abnormalities induced the stagnation of digested foods and possibly offered a favorable site for abnormal proliferation of the related agents and alcohol fermentation. *Candida* group is a symbiotic yeast, and present in the gastrointestinal tract. Moreover, it's a dimorphic organism, existing as a normal yeast-like organism and an invasive fungal form. Retrospective analysis showed that *Candida albicans* was the most common causative agent in patients with Gut Fermentation Syndrome.

In some cases, no gastrointestinal abnormality was found. On this occasion, secondary disturbances of the normal intestinal flora due to the frequent medical antibiotics using seems to be another important factor.

Case history

A 30-year-old male was firstly sent to our clinic because of intoxication without ethanol intake at November, 2011. In his medical history, he had at least a four-year history of recurrent unexplained gastrointestinal discomfort, intoxication and abnormal liver function tests. He recalled that 4 years ago while he was disposed to bouts of upper abdominal discomfort, he went to local hospital and was found to have elevated transaminase more than 4 times the upper limit of normal (ULN). He did not have a history of chronic liver disease, alcohol abuse, and illicit drug use. Serological detection of hepatitis viruses, Epstein-Barr virus and Cytomegalovirus showed all negative. Screening results of autoimmune and metabolic liver diseases were also negative. Hepatic ultrasound revealed mild fatty liver. Since these episodes were mild and largely self-limited, he had not sought for further medical examination and only took some intravenous administration of hepatoprotective medications. One month later, his liver function returned to normal. However, after half a month, laboratory test values highly elevated aminotransferases (ALT: 731U/L [18*ULN]; AST 368U/L [9*ULN]) and γ-GT levels (256.7U/L [5*ULN]) again. Because of concern for an underlying liver disease, the patient underwent core needle biopsy. The histopathology only revealed steatohepatitis, so he continued to receive intravenous administration of hepatoprotective drugs. Then liver enzymes declined gradually. Over the next 6 months, laboratory evaluation revealed relatively normal liver function, but he developed recurrent nausea and acid regurgitation at August, 2012. His above symptoms got aggra-

vated and accompanied by somnolence. During symptomatic periods, he usually refused to see a doctor and drunk lots of water to induce vomiting. Then symptoms were relieved quickly, but liver enzymes elevated obviously in the following days (more than 10*ULN). At the same time similar episodes became more persistent and frequent.

In order to research his etiology, several further examinations were performed. The gastroscopy revealed reflux esophagitis (grade LA-B), superficial gastritis, and Helicobacter pylori (HP) infection. Histopathology of gastric biopsy only indicated chronic inflammation. Although the HP eradication treatment was provided, his symptoms were not improved after therapy.

At June, 2013, the patient became intoxicated as reported by his family members, and his symptoms could be improved quickly after taking plenty of water and heavy vomiting. Then, he went to two psychiatric clinics and was diagnosed as nervous vomiting and depression. Moreover, he was treated with Sertraline and Alprazolam for 6 months but without any improvement. His condition got progressively and deteriorated. The episodes of intoxication could last for five to seven days each time, and even twice a month. About one and a half year ago, his urine turned dark, and the total bilirubin levels rose to 81.3 umol/l (4.5*ULN). The patient complained of dizziness and his headaches got worse. His family members described that he had fall unconscious twice and became somnolent in most days. At the second time, he was sent to the psychiatry department. He was completely drunk appearance without consciousness. However, he fully recovered by the next day. He denied any alcohol intake and his family members testified that.

Based on the above clinical manifestations, like the history of intoxication without drinking, he was suspected to be Gut Fermentation Syndrome on admission to our hospital. The blood alcohol concentration (BAC) was tested when he had intoxicated behavior, in this time his BAC rose to 311.2 mg/dl. Meanwhile, Candida parapsilosis were detected twice using cultures of stool. The patient was finally diagnosed as Gut Fermentation Syndrome. He was treated with oral Fluconazole 150 mg/day and Bifico six tablets/day according to the drug resistance results (April, 2014). During the treatment period, dietary restriction was performed. After 10 days of therapy, the episodes began to decrease in severity and frequency. The liver enzymes also declined (ALT: 30-140 U/L; γ-GT: <300 U/L). Three months later, the patient's condition improved significantly with mild abnormal liver function though mild attack intermittently, so his therapy was switched from Fluconazole to Voriconazole 400 mg/d plus Nystatin 200 MU/d for two weeks. After two weeks therapy, the patient still had mild intoxication, so he stopped using all medicine. Two months later he had another mild intoxication and abnormal liver function and relieved without any treatment in one week. From that time to now he never had any symptoms intoxication with stable liver function (**Table 1**) and got married in 2016 with a healthy baby.

Discussion

This patient was young and without any basic disease. His main clinical manifestations were recurrent gastrointestinal discomfort and somnolence. Helicobacter pylori infection was detected with gastroscopy, but therapy for anti HP didn't improve his symptoms. Breath and blood ethanol concentrations of him were all elevated during symptomatic periods, and surreptitious drinking could be rule out under strictly monitored by his families and doctors. Moreover, the stool cultures demonstrated the causative organism as Candida parapsilosis and sensitive to antifungal agent therapy, which further confirmed the diagnosis.

Eaton [12] has described these patients as "thick folder", because they have usually been seen in several departments. Their clinical manifestations were non-specific or slight at the beginning of the disease. The routine clinical examination and standard laboratory tests revealed nothing of specific note, so resulting in delayed diagnosis. The case we reported here, his initial symptoms can be relieved after heavy vomiting, so he was once misdiagnosed as general gastrointestinal disease and mental illness until the typical drunkenness-like symptoms appeared but without accessment for alcohol. The doctor suspected of this syndrome, then carried out the relative examination and made final diagnosis.

After each episode, the obviously elevated level of liver enzyme was the feature of this patient,

Table 1. The results of liver function

Year	Month	Day	ALT	AST	r-GT	TBIL	DBIL
2011	10	12	129	117	98.2		
	11	30	731	368	256		
2012	1	19	76.6	56.4	102.8		
	3	25	49	35.3	58.7		
	7	3	128.6	123	102.3		
	8	3	474.4	402.8	278.9		
	8	17	185.3	106.5	159.2		
	9	3	48.8	30.3	84.4	23.17	3.68
	10	8	163.4	119.3	111.3		
	11	12	107	170	157		
	12	26	877	965.9	940.7		
	12	11	229.2	443.5	434.3	25.3	11.3
	12	27	877	965.9	940	26.9	
2013	1	7	349.2	160.7	375.3		
	1	24	247.8	220.5	251		
	2	17	184.9	150.5	270.2		
	3	26	168.2	59.7	194.1		
	4	15	117.6	245.1	218.8		
	5	22	189	419			
	7	7	107	404	343	26	6.74
	7	23	41.6	51.3	311		
	8	13	116.9	235.1	649.6		
	8	30	149.4	156.5	218.8		
	9	7	58.6	235.4	300	35.9	11.3
	10	5	351.8	250.1	411.2		
	10	28	47	58.3	190		
	11	12	23.2	116.8	322.1	41.9	17.2
2014	4	2	49	170	982	17.6	8
	4	9	178	226	625	9.1	4
	4	16	145	108	406		
	5	1	16.6	61.4	490.5		
	5	17	21.4	67.7	496.5	21.4	12.7
	5	23	74.4	211.9	605.8		
	5	28	143	179			
	6	5	49.4	98.1	315		
	6	16	103.5	125.1	397.6		
	7	10	25	25	120		
	9	9	122.8	128.1	85		
	10	20	30	28	90		
2015	1	6	28	30	58		
2016	2	10	25	24	60		

and improved quickly accompanied with the relief of symptoms. The liver histological findings only revealed steatohepatitis. In all cases have been reported, only one patient with mild liver dysfunction have been mentioned from Japan in 1976 [13], the others were normal or didn't affect liver function. It was speculated that the overgrowth of yeast in the gut induced fermentation of carbohydrates into endogenous ethanol, and then caused alcoholic liver injury, flatulence, and vomiting. Because of individual differences in ethanol metabolism, someone may develop alcohol-induced liver injury. Although Mezey [14] *et al* suggested that it's unlikely that intestinal endogenous ethanol production has a significant effect on the pathogenesis of liver disease, but we strongly disputed their conclusion, because of there were significant correlations between the onset of digestive discomfort or intoxication and the peak levels of elevated liver enzymes in this patient. In all cases have been reported, most patients have various abnormalities of intestinal anatomy or antibiotics abuse. Mezey [14] *et al* found endogenous ethanol production in one third of patients after jejunoileal bypass operation for morbid obesity, and a similar occurrence was identified in an animal model. These abnormalities may cause the stagnation of digested foods and possibly offer a favorable place for alcoholic fermentation. Otherwise, the frequent medical use of antibiotics could induce dysbacteriosis of the intestinal microflora and abnormal proliferation of the related agents [15]. However, we report the case without any above predisposition. In previous reports there were also some cases without above factors. We think some other factors increasing the risk of gut fermentation and the underlying mechanisms needed to explore, such as microbiological floras in small bowl, fermentation process and so on.

Although antifungal agent therapy and decreased carbohydrate intake have resulted in the successful resolution of symptoms in many cases, individual therapy is still preferred. In some cases, the symptoms may disappear spontaneously, which implies that administration of antifungal therapy should be cautious since their potential adverse effects. Furthermore, surgical treatment of intestinal stenosis or removing place for fermentation is the key solution for some patients.

The process of diagnosing Gut Fermentation Syndrome is usually time consuming and dramatic. So far, the diagnosis of this syndrome is typically based on the presence of host fac-

tors, such as altered GI anatomy, symptoms of inebriation, elevated blood alcohol level, and GI cultures showing an elevated yeast burden. Nevertheless, whether the causative agents of this syndrome are yeast alone or accompanied with bacteria, moreover, it has been a controversial issue. Most reported cases were associated with abnormal intestinal yeast proliferation, especially Candida group, therefore, further study is needed. Sugars production almost through glycolytic, pentose phosphate and Entner-Doudoroff pathways induced by bacteria ferment, their major end products extremely lactic and pyruvic acids. However, common yeasts are able to ferment sugars through the homolactic, heterolactic or mixed acid fermentation pathways, with ethanol as the major end product. So, we speculate yeast may be the most likely cause of his disease.

As a rare disease, clinicians, toxicologists and forensic scientists should be aware of this syndrome because its related social implications, such as loss of job, relationship difficulties, and even possible arrest. Health care providers should think more about patients with non-specific or unexplained neurological symptoms. Moreover, these intoxicated patient who denies ingesting alcohol or even some patients with altered GI anatomy who complained of digestive discomfort.

Disclosure of conflict of interest

None.

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