

Sensitization to Beer Ingredients in Chinese Individuals with Beer Allergy: A Clinical Study of 20 Cases

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Key Words

Allergy · Beer · Barley · Hops · Sorghum · Yeast

Abstract

Background: Rare case reports of allergic reactions to beer have been published, but the nature of the eliciting substances in beer ingredients is often unknown. **Objective:** It was the aim of this study to identify sensitization patterns against various beer ingredients in Chinese individuals with beer allergy. **Methods:** Twenty-seven Chinese individuals with a clear-cut history of beer allergy were prescreened to answer a specific questionnaire related to the history and symptoms of beer allergy. Twenty individuals underwent allergy diagnostics with different food allergens and extracts of beer ingredients using the skin prick test (SPT) and the open oral provocation test (OPT) with beer. **Results:** Fifteen patients (75%) showed positive reactions to one or more beer ingredients. Of these, 9 individuals, reactive to sorghum

and/or sorghum malt also showed positive reactions to other ingredients. Seventeen individuals showed variable symptoms after the OPT. Cutaneous erythema and urticaria were the most common symptoms and usually persisted for over 2 h. There were no significant differences in SPT reactivity to beer ingredients between male and female individuals. Single patients reacted to barley, hops or yeast. **Conclusions:** Sensitization to sorghum and/or sorghum malt was the most common finding in Chinese individuals with beer allergy.

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Introduction

Beer has been part of human culture since ancient times. Although beer is produced and consumed all over the world, allergic reactions are rarely reported. Until now, only some case reports of beer allergy have been published [1–11], describing immediate (type I) hyper-

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sensitivity reactions such as pruritus, urticaria, dyspnea, or anaphylaxis after beer consumption. In addition to a true allergy to beer ingredients, other triggers such as food allergens in side dishes including peanuts, seafood, soy, wheat, or spices [12], food additives (coloring dyes) or preservatives (sulfites) [13, 14] and alcohol (ethanol and its derivatives from other sources) [4, 15, 16] may also be responsible for the allergic reaction.

The main ingredients of beer used for the brewing process are water, malts, yeasts, and hops. Beer produced outside Germany without adhering to the 'Bavarian Beer Purity Law' from 1516 [17] may contain other cereals such as rye, rice, wheat, corn, or less commonly potatoes and other vegetables like peas.

Due to an accelerating globalization of the Chinese economy, beer consumption soars while most of the local breweries adopt western standards in beer brewing. Beer allergy has been repeatedly mentioned in local press reports and is believed to be not uncommon, though lacking confirmation by well-designed clinical studies. In the current study, Chinese individuals with past histories of beer allergy were examined. After a thorough questionnaire study, a skin prick test (SPT) with different extracts of beer ingredients and food allergens and an open oral provocation test (OPT) with native beer were conducted with the aim to identify the sensitization patterns.

Materials and Methods

Study Design

This was a prospective open clinical study recruiting patients with a history of beer allergy out of a total of approximately 160,000 individuals who came to the outpatient clinic of the Department of Dermatology, Southwest Hospital, Chongqing, China, between July 2010 and October 2011. After careful evaluation of the medical history, individuals suspected of allergic reactions related to beer consumption were prescreened and selected for examinations of sensitization to beer ingredients and food allergens as well as for an open OPT with beer, as illustrated in figure 1. Ten healthy volunteers without any discomfort after beer consumption were also selected as controls. The study was approved by the ethics committee of the Southwest Hospital prior to the start of the study.

Questionnaire

All the enrolled individuals fulfilled a specific questionnaire regarding age, sex, previous medical history, family and personal history of allergy, as well as information about possible allergic reactions related to beer consumption, such as the types of allergic symptoms, the time interval between beer drinking and the appearance of symptoms, numbers of episodes, volume of beer consumption, concurrent foods taken, and family history of allergy to beer and other alcoholic beverages.

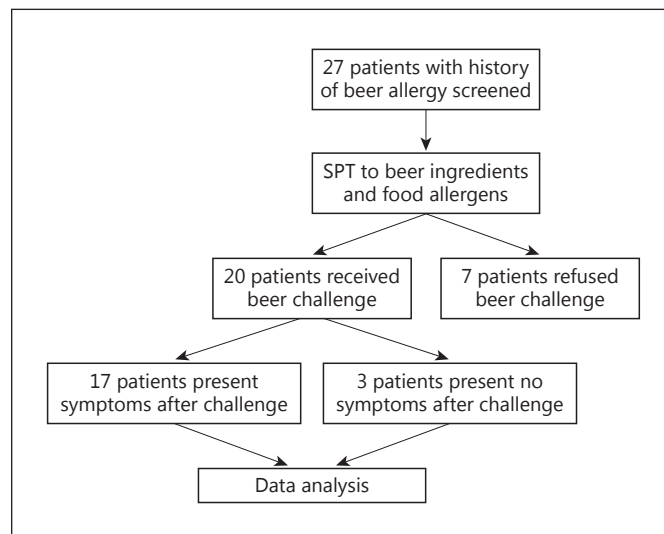


Fig. 1. Study design, summary of progress and flowchart of the individuals with beer allergy. Twenty-seven individuals with a history of beer allergy were recruited, and 20 of them underwent the open OPT with the lager beer.

Possible Allergens in Beer Ingredients

Twelve raw materials used for beer brewing, including sorghum, sorghum malt, millet, millet malt, barley, barley malt, maize, maize malt, yeast (*Saccharomyces cerevisiae*), hops (*Humulus lupulus*), protease (Brewers Clarex™, DSM, Heerlen, The Netherlands) and brewery yeasts (bottom fermented) were extracted as described previously and prepared for the SPT [17]. The materials applied in the present study are listed in table 1.

Skin Prick Test

The SPT was performed with the extracts mentioned above and native beer (Chongqing Beer™, Chongqing Brewery Co., Chongqing, China), as well as with commercially available common food allergens (Allergopharma™ Skin Prick Testing Kits, Reinbeck, Germany) including 20 kinds of common food allergens (table 1). Histamine phosphate at 10 mg/ml and normal saline were used as positive and negative controls, respectively. Short-acting antihistamine was avoided at least 3 days prior to the SPT, and long-acting antihistamines or immunosuppressants were withdrawn at least 1 month before the test. The result was assessed as positive if the wheal was ≥ 3 mm with erythema, occurring 15 min after testing, with the normal saline being negative at the same time.

Oral Provocation Test

The OPT was performed as described above [18], with incremental doses of 50 ml of beer every 15 min (to a maximum of 0.5 liters), starting with 50 ml. Both subjective symptoms and objective signs were carefully recorded after each dose. The clinical symptoms were considered as 'positive reactions' when objective symptoms (oral, skin, gastrointestinal, respiratory, and/or cardiovascular) were observed by the investigators during the provocation. In the case of subjective symptoms such as itchiness, ab-

dominal pain or throat tightness, the provocation was temporarily interrupted until either complete resolution of symptoms or appearance of typical objective symptoms. If symptoms resolved spontaneously, the previous dose was repeated. All individuals were observed for 24 h after the OPT. If no reaction occurred after this period, the provocation was considered negative.

Statistical Analysis

Prevalence was calculated for patient characteristics (sex, age group) in all studied individuals. Fisher's test was used to analyze possible significant differences. Quantitative data, with and without normal distribution, were analyzed using the unpaired t test or Mann-Whitney U test, respectively. Data were expressed as the mean $\pm$ standard deviation. All statistical analyses were performed using SPSS for Windows version 13.0 (Chicago, Ill., USA). $p < 0.05$ was considered statistically significant.

Results

A total of 27 individuals (18 males and 9 females, mean age 29.9 ± 6.8 years) with a history of hypersensitivity symptoms after beer consumption were prescreened out of a total of 160,000 outpatients in the years 2010–2011. All individuals reported similar episodes of hypersensitivity symptoms after beer consumption repeatedly for more than 5 times. Of these, 20 individuals who gave informed consent to oral beer provocation tests were included for further analysis.

Among patients undergoing provocation tests, 4 individuals (20%) had a previous history of chronic urticaria, 3 individuals (15%) of allergic rhinoconjunctivitis, 1 subject had a previous allergic reaction to penicillin and 1 to tetanus antitoxin, but all without further allergological confirmation. The demographic and clinical features of the individuals are summarized in table 2.

In the SPT, 15 individuals (75%) revealed positive reactions to ≥ 1 beer ingredient. Among them, 3 individuals (20%) were positive to 1 beer ingredient, 8 (53.3%) to >2 ingredients and 7 (46.7%) to >3 ingredients. As for the sensitized allergen in individuals with positive SPT to beer ingredients, 11 individuals (73.3%) showed positive reactions to native beer, and 9 individuals (60%) who reacted to sorghum and/or sorghum malt also showed positive reactions to other ingredients. As for other allergens, 7 individuals (46.7%) showed a positive reaction to millet and/or millet malt, barley and/or barley malt, and 5 individuals (33.3%) to yeast and hops. All control volunteers were negative in all beer ingredients tested.

Moreover, there were differences in beer ingredients extracted with different methods. For example, 5 individuals with a positive OPT showed positive reactions to sor-

Table 1. Beer ingredients and common food allergens tested in the present study

<i>Beer ingredients</i>	
Sorghum crude extract	Barley crude extract
Sorghum fine extract	Barley fine extract
Sorghum extract	Barley extract
Sorghum malt crude extract	Barley malt crude extract
Sorghum malt fine extract	Barley malt fine extract
Sorghum malt extract	Barley malt extract
Millet crude extract	Maize crude extract
Millet fine extract	Maize fine extract
Millet extract	Maize extract
Millet malt crude extract	Maize malt crude extract
Millet malt fine extract	Maize malt fine extract
Millet malt extract	Maize malt extract
Yeast	Hops, type 90 pellets
Hops, type 45 pellets	Isoextract with 30% iso-alpha acids
Hops oil containing 90% linalool	Hops oil containing 70% 2-phenylethanol
<i>Foods</i>	
Hazelnut	Celery
Rye	Beef
Egg	Milk
Chicken	Wheat
Pork	Soy bean
Apple	Avocado
Potato	Rice
Crab	Latex
Peanut	Trout
Tomato	Carrot

ghum malt extract, meanwhile only 3 individuals showed a positive reaction to sorghum extract. Such findings were also observed for other ingredients, such as barley and barley malt, millet and millet malt (data not shown).

Six out of 20 individuals (30%) revealed a sensitization to various food allergens. Among them, 3 individuals (15%) were positive to rye flour, 2 (10%) to crab and 1 (5%) to egg, celery, trout, and chicken. No reaction was detected for apple, tomato, avocado, rice, or latex. However, none of these individuals with IgE sensitization to food allergen reported actual symptoms of food allergy after consumption of the suspected food alone.

Various symptoms were observed in 17 individuals after the OPT with the incriminated beer (fig. 2). Of those with a positive OPT, 13 cases showed a positive SPT to various beer ingredients, and the most common sensitized allergens included sorghum (53.8%), barley (46.2%) and millet (46.2%). Two out of 3 individuals with a negative OPT also showed positive SPT reaction to beer ingredients (cases No. 5, 14 and 20).

Table 2. Clinical and laboratory characteristics of 20 individuals with beer allergy

Patient No.	Age, years/sex	Reported symptoms after beer consumption	Reported allergic reactions to other alcoholic beverages	Symptoms after beer provocation	Time interval ¹	Volume of beer ² , ml	Positive beer allergens ³	SPT with native beer	Positive food allergens
1	29/M	cutaneous erythema and itch, papular eruption	none	erythema and itch	12 min	50	yeast	negative	negative
2	29/F	cutaneous erythema and itch, papular eruption	none	urticaria	40 min	200	negative	positive	negative
3	23/M	cutaneous erythema and itch, papular eruption	Chinese liquor	urticaria	65 min	250	sorghum, hops	positive	negative
4	29/F	cutaneous erythema and itch	red wine	urticaria	35 min	150	barley, hops	positive	negative
5	40/M	papular eruption	none	none	none	500	barley, sorghum	positive	negative
6	30/M	cutaneous erythema and itch, urticaria and angioedema	Chinese liquor	urticaria	35 min	200	sorghum malt, millet malt	positive	rye
7	22/M	cutaneous erythema and itch, papular eruption	none	papular eruption	10 h	500	hops, barley malt	negative	negative
8	23/M	cutaneous erythema and itch, headache, dizziness	none	erythema	15 min	50	barley, hops	positive	negative
9	24/M	gastrointestinal symptom, cutaneous erythema and itch	no	urticaria	80 min	300	yeast	positive	negative
10	44/F	cutaneous erythema and itch, urticaria and angioedema	red wine	urticaria and labial angioedema	35 min	150	barley, sorghum, sorghum malt, millet malt, yeast	negative	rye
11	26/F	urticaria and angioedema	none	urticaria	60 min	350	negative	positive	negative
12	36/M	gastrointestinal symptom, cutaneous erythema and itch	red wine	erythema and itch, urticaria	50 min	300	sorghum malt, millet malt	positive	rye
13	20/M	cutaneous erythema and itch, urticaria and angioedema, papular eruption	Chinese liquor, white wine	erythema and itch, urticaria and periorbital angioedema, nausea and emesis	2 h	450	barley, barley malt, sorghum, sorghum malt, millet malt, hops	positive	eggs, chicken
14	38/M	gastrointestinal symptom, cutaneous erythema and itch, papular eruption	Chinese liquor, red wine	none	none	500	sorghum malt, millet, millet malt yeast	positive	crab, trout, celeriac
15	26/F	cutaneous erythema and itch, papular eruption	red wine	papular eruption	12 h	500	negative	negative	negative
16	23/F	cutaneous erythema and itch, urticaria and angioedema, papular eruption	none	urticaria	20 min	300	barley, barley malt, sorghum, sorghum malt, millet, millet malt yeast	positive	negative
17	38/M	cutaneous erythema and itch	none	erythema and itch	20 min	150	hops	positive	negative
18	25/M	gastrointestinal symptom, cutaneous erythema and itch, papular eruption	none	urticaria and labial angioedema	15 min	100	millet sorghum malt	negative	crab
19	39/M	gastrointestinal symptom, cutaneous erythema and itch, headache	Chinese liquor	erythema without itch	30 min	200	negative	positive	negative
20	22/M	cutaneous erythema and itch, urticaria and angioedema	Chinese liquor	none	none	500	negative	negative	negative

¹ Time interval between the appearance of symptoms and the OPT with beer. ² Volume of beer drunk after which the hypersensitivity symptoms appear. ³ Beer allergens showing positive reactions in the SPT.

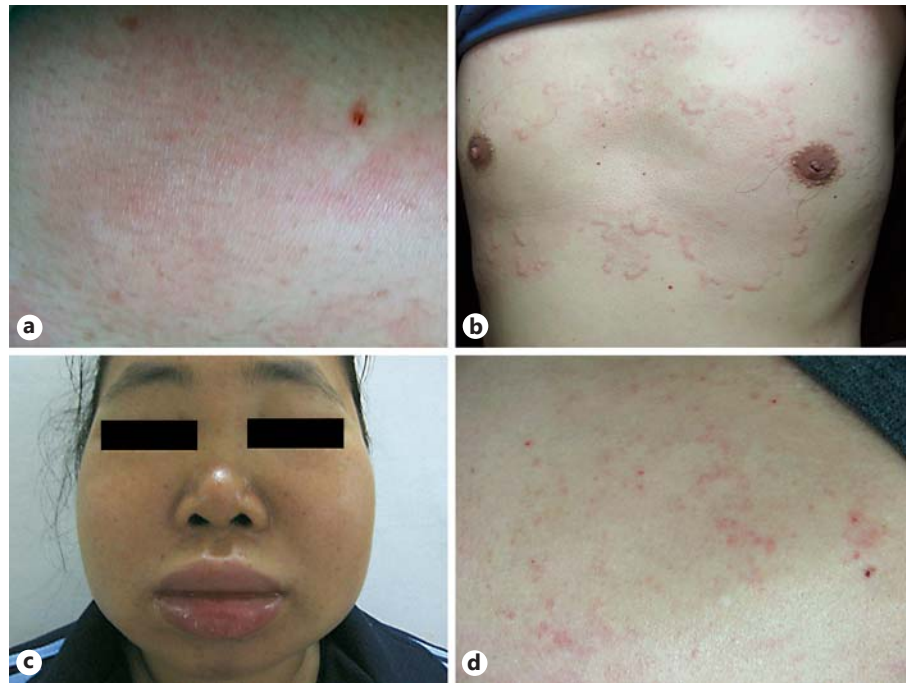


Fig. 2. Hypersensitivity reactions occurring after the oral beer provocation test. **a** Erythema on the back occurring 15 min after provocation (case No. 8). **b** Urticaria on the trunk occurring 35 min after provocation (case No. 6). **c** Labial angioedema occurring 35 min after provocation (case No. 10). **d** Papular eruptions in the abdominal area occurring 12 h after provocation (case No. 15).

The types of reactions and the time intervals between the OPT and the appearance of symptoms are shown in table 2. In patients with a positive OPT, 6 individuals (35.3%) showed cutaneous erythema with or without itch, 8 individuals (47.1%) presented urticaria with or without angioedema, and 1 patient presented both cutaneous and gastrointestinal symptoms. Furthermore, 15 individuals (88.2%) developed an allergic reaction within 2 h after the OPT, and 2 (11.8%) individuals (cases No. 7 and 15) who were challenged with the maximal volume of beer showed papular eruptions after 10–12 h. The mean volume of beer inducing hypersensitivity reactions was 247.1 ± 141.9 ml (range 50–500). On the other hand, 3 men with a history of allergy after beer consumption did not show any discomforts and symptoms after they had drunk 500 ml in the beer provocation test.

Among individuals with positive OPT results, no statistical significances could be observed for (1) gender difference ($p = 0.13$), (2) the percent of positive SPT to food allergens between individuals with and without sensitization to beer ingredients ($p = 0.26$), (3) the mean age of the individuals with or without sensitization to beer ingredients ($p = 0.76$), and (4) the percent of positive SPT to beer ingredients and positive SPT to native beer ($p = 1.0$).

Discussion

Despite its worldwide consumption, allergic reactions to beer have rarely been reported, especially those via an IgE-mediated pathway [1–16, 18]. The real prevalence of IgE-mediated allergic reaction to beer in the general population is unknown. So far, there are only 8 cases published in the English literature [8–11, 18, 19]. However, most of the reported cases were not confirmed by SPT due to the lack of proper extracts from beer ingredients [18]. Only 3 cases were confirmed by SPT with beer extracts and 1 with commercial barley extract [10, 11], as well as 3 cases with native beer [8, 9, 18]. Determination of specific IgE antibodies directed to part of the beer ingredients has been done in 1 case [8]. As beer is usually consumed with side dishes, exclusion of food allergy or intolerance to food additives is important for the diagnosis [6, 9].

In the present study, 17 individuals (85%) with a history of beer allergy presented various allergic symptoms after the open oral beer provocation test, but only 14 cases (70%) showed positive reactions to native beer and 15 (75%) revealed positive reactions to ≥ 1 beer ingredient, which implies that the OPT is more sensitive in the establishment of diagnosis for beer allergy. Further, 75% of individuals with a history of beer allergy were positive to ≥ 1 beer ingredient, but only 30% revealed a sensitization to

various food allergens. Double sensitizations to both beer and food were seen in 6 individuals.

Although papular eruptions could be observed in 2 cases after 10–12 h during the OPT, which indicated late-phase hypersensitivity reactions, most cases presented immediate hypersensitivity reactions, such as erythema and urticaria, which is in line with their history and previous studies [1, 2, 5–11]. The urticarial and pruritic nature of the lesions, the occurrence within 2 h after the OPT, the previously recurrent episodes, and the positive SPT indicate an IgE-mediated allergic reaction. Moreover, the doses of beer used for provocation in the present study ranged from 50 to 500 ml, while the occurrence of clinical reactions is independent of the volume of beer taken in our study. This can be indirect evidence to rule out sulfite intolerance as a possible trigger factor in our individuals, as the relevant reactions to preservatives are mostly dose related.

In contrast to most previous single case reports on beer allergy with barley as the culprit allergen, sorghum and/or sorghum malt was most commonly detected in our series, followed by millet, barley, yeast, and hops. A possible explanation is that Chinese liquor (distillate spirit) is usually produced with sorghum or maize and its sensitization may have already been induced through early consumption for drinking or cooking. Moreover, sorghum and rice are often added to barley for beer brewery in China to lower the cost of production. Although studies addressing allergic reactions to Chinese liquor could not be found in medical literatures, such cases, like beer allergy, have been repeatedly mentioned in local press reports and observed in our clinical practices. As sorghum belongs to the Poaceae family and cross-reactivity between cereals and grasses are common in patients with nasobronchial allergy [20, 21], an association with grass pollen allergy is possible in our patients with beer allergy. Although we did not test our patients for grass pollen allergy, most of them did not have clinical symptoms of pollen allergy, and 3 individuals with allergic rhinoconjunctivitis have previously been confirmed with sensitization to dust mite by the SPT.

More interestingly, our individuals with beer allergy show different positive rates to the same beer ingredients with a different extract process. It seems that malts of cereals are more 'allergenic' than its natural components. A possible explanation is that the allergens responsible for reactions may undergo changes or the formation of new antigens/epitopes during beer production, when the cereal kernel is germinated, roasted, boiled, or fermented for its different further uses [3]. Another possibility is that there are more concentrated allergens in malt extracts after

related processes. Further studies including sodium dodecyl sulfate polyacrylamide gel electrophoresis and immunoblotting assays are warranted to investigate possible common allergens in beer, sorghum and sorghum malt.

It is noteworthy that some of our individuals with a clear history of beer allergy and a positive OPT but with negative results of the SPT reported urticarial reactions to other alcoholic beverages such as wines or Chinese liquor. Allergic reactions (immunologic or non-immunologic) to ethanol or its derivative acetic acid should be tested and ruled out in such cases in future studies [4, 15, 16]. Three individuals reporting beer allergy did not show any symptoms after oral provocation. According to their description, hypersensitivity symptoms appeared only after consumption of >1 liter of beer. Further investigation is needed to determine if their reactions are IgE mediated or not.

Several proteins with different molecular weights have been implied as the main allergens in beer, including barley lipid transfer protein (LTP; 10 kDa) [18], protein Z4 (45 kDa) [22], a 18-kDa protein originated from barley [19, 23], a protein of approximately 35 kDa in wheat extract [8], and another of 38 kDa in beer extract [11]. The LTP, which can cross-react with LTP from several other plants [24, 25], could be present in the barley kernel surviving the malting and brewing process [18]. Beer LTP can be found intact in the beer as one of its main protein components.

Our results raise several questions: (1) are there any similar or new proteins in Chinese beer which may cross-react with sorghum? (2) Are the underlying allergens different in different beer brands containing different ingredients in addition to barley? (3) How about the genetic background of individuals prone to beer allergy? To answer these questions, molecular studies such as immunoblotting of serum samples and surveying of genetic polymorphisms may be helpful.

In conclusion, beer allergy is not a rare condition in the Chinese population. Cutaneous erythema and urticaria are the most common symptoms and usually present within 2 h. Sensitization to sorghum and/or sorghum malts is most common but not sensitization to barley, as reported in the literature.

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