Chapter 3

Perspectives to take into account when Studying Celiac Disease in China and Central America

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Doi: http://dx.doi.org/10.3926/oms.237

How to cite this chapter

Perez Villavicencio A, Beirute Lucke C, Peña AS. Perspectives to take into account when Studying Celiac Disease in China and Central America. In Rodrigo L and Peña AS, editors. *Celiac Disease and Non-Celiac Gluten Sensitivity*. Barcelona, Spain: OmniaScience; 2014. p. 61-74.

Abstract

Until quite recently, it was thought that celiac disease existed neither in China nor in Central America. The cultivation of rice in China and the cultivation of maize from the Mexican highlands have respectively been the basis of nourishment in China and Central America. Environmental, social and cultural changes in these regions allow foreseeing an increase of patients with celiac disease in both regions of the world. By way of example, we can point to the deworming of rural populations which contributes to a change in the TH2 to TH1 predominant intestinal immune response, changes in the intestinal microbiota, mainly in urban areas due to access to antibiotics, change in dietary habits due to the influence of “fast foods” and changes in traditional diets based on rice or maize due to the diffusion of diets with a higher gluten content. However, it is necessary to analyze difficulties in these countries regarding the identification of the disease as well as the techniques involved in its diagnosis. The main limitation of these studies lies in the absence of duodenal biopsy specimens. In fact, every population where celiac disease is thought to be emerging needs to adjust its array of detection procedures. Although it is true that sensitive and specific serologic tests for celiac disease have allowed greater confidence in establishing the prevalence of this disease in European and North American studies, the information from China and Central America is still scarce. The creation of interdisciplinary study groups is necessary to design specific protocols for each region.

1. Introduction

Until relatively recent times it was thought that celiac disease existed neither in China nor in Central America. Sporadic cases have been described in both continents and brief series of studies on the subject have been published in China, but not in the Central American countries, with the possible exception of Panama.

Rice cultivation in several regions of China and maize cultivation from the Mexican highlands have been the dominant staples in China and Central America, respectively, while potato cultivation was developed in the Peruvian Andes.

A Canadian university hospital in Vancouver[1] found in Asian-descended populations living in North America, from 1982 to 2002, that celiac disease was diagnosed in fourteen of these persons. Eleven were indo-Canadians, including ten with Punjabi ancestry and one Chinese patient.

Paleo-botanic evidence suggests that populations in north China could have been exposed to gluten-containing cereals for longer than it was recently thought. Findings made in August, 2010[2] suggest that the introduction of wheat in China could date from 2,500 B.C., but may have started to become significant about 2,000 B.C. Nowadays, China is a world-class center of wheat production, which encompasses its northern and southern regions. After the Han Dynasty (206 B.C.–A.D. 9), wheat became one of the main staples in northern China[3]. Since the Northern Song Dynasty (A.D. 960–1,127), wheat was also introduced in southern China.[4] In order to gain a better understanding of the impact of wheat in the presence of CD in China, it is necessary to compare it to rice and to frame both plants within the historical context of the nation. There are weighty reasons, relative to the nature of each of these grains, which made rice preferable in central and southern China: It can produce grains for up to three decades, grow on level land as well as on slopes and it has very high yields. Rice requires large quantities of water, especially due to the strategy of flooding the rice fields in the early stages of cultivation, which prevents the growth of other harmful plants and the arrival of certain pests (it is feasible to cultivate it without flooding the fields, but not doing so makes eventual plague control and fertilization more difficult). These requirements fit well with central and southern China's hydrography, regions that have the large Yangtze and Huanghe rivers and their enormous network of tributary streams, which provide enough water for widespread and intensive rice cultivation.

Chinese populations developed rice agriculture around 7,500 B.C. From this date onwards, this new means of subsistence slowly spread through Northern China until, around 2,100 B.C., the first Chinese state emerged, the Xia Dynasty, whose historicity is still being debated. With the next Dynasty, the Shang (1,800–1,027 B.C.) we stand on firm historical ground. This dynasty was an island of greater organization in the midst of a patchwork of other smaller-scale societies, whose influence and prestige, by means of a process of cultural diffusion, contributed to the spread of Shang culture (the basis of what today is known as China) among the diverse culture groups which, with the passing of millennia, were absorbed into the mainstream of Chinese culture.

The Shang collapse, still not fully understood, was probably brought about in part by the rise of another state, the Western Zhou Dynasty (1,027–771 B.C.), which assimilated the cultural and

organizational achievements of their predecessors, consolidating and expanding their cultural influence.

The Zhou, however, were not able to keep direct control of the areas under their influence and, for the period spanning from 771 to 221 B.C., the Zhou sovereign was only the *de jure* ruler of the region. This could have arisen partly from what seems to have been a feudal system in which noblemen of diverse ranks were granted lands, which they ruled in the name of the king. With the passing of the centuries, these feudal lands acquired more and more power and independence up to the point where each one could have become an autonomous state in its own right.

Each one of these states, even when they initially paid nominal homage to the authority of the Zhou ruler, eventually came to develop its own political agenda. On the other hand, it is also likely that other states may have arisen by means of the diffusion of Zhou culture and achievements, which may not necessarily have been originally feudal vassals of the latter.

In any case, the second half of the Zhou period, known as the Warring States Period (as its name implies) was plagued by constant war. Towards the year 221 B.C., Shi Huangdi, ruler of the State of Qin, finally defeated all his opponents and became the first emperor of all of China, unifying for the first time writing, measurements and administration and finally managing to bring peace to the country.

However, the highly autocratic style of Qin administration generated great unrest and opposition and, by the year 207 B.C., this led to the collapse of the Dynasty.

The following dynasty, the Western Han (207 B.C.–A.D. 9), availed itself of the structure and administrative achievements of the Qin and it was the first which managed to impose a stable and relatively peaceful rule over almost the whole country, which laid the foundations for further growth. China's ethnic majority calls itself the "sons of Han" or simply the "Han". This stability generated the country's elevated demography,[5] which has been one of its defining features ever since. Within this historical context, possessing rice and enough water, China has been able to adequately satisfy its nutritional needs.[6]

North China, however, lacking a bountiful irrigation and having a less humid climate, was forced to depend more on grains adapted to drier climates, among which wheat stands out. Cultivation of this grain began to be given an emphasis since the nineteen thirties, midway through the short-lived Chinese Republic, an initiative that has been maintained and increased under the People's Republic of China.

Given rice's high water requirements, it would be reasonable to look for supplementary crops, which would require less water so as to be able to lessen the demand of this resource. China has had powerful reasons to become the world's foremost wheat producer and consumer. This country, in recent years has produced yearly some 115 million metric tons of wheat, about 40% more than India, the second biggest producer, and accounting for 17.06% of the world's total output.

This wheat, most of which is for internal consumption, must be having a widespread diffusion through massive consumer products. This is potentiated by China's insertion in the world market.

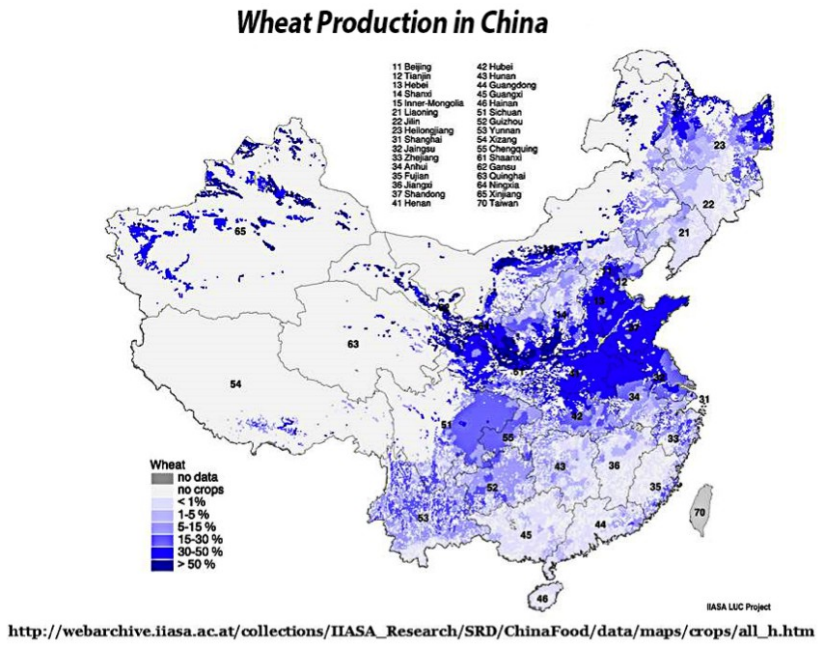

Figure 1. Wheat Production in China

In spite of the lack of data on the subject, the prevalence of celiac disease in China and Japan is foreseeably low, due to a rice-based diet. However, with the traditional staple of rice slowly being replaced by western style food, which has a high wheat content,[7] celiac disease could become a health issue in China.

A similar situation is foreseen in Central America; however, in some small towns, which are distant from the capitals, a relatively gluten-free diet may still be widespread.

2. Current situation in China

Currently, the Chinese eat several kinds of wheat-derived products: noodles, steamed bread and cakes, to name a few. China has a long history of consuming *mianjin* or *kaofu*, which are basically gluten-based products. Wheat is the second leading cereal crop in China in terms of cultivated surface and production. More than 90% of this wheat grain is used to make steamed bread and noodles. Even though wheat is cultivated in twenty nine out of thirty Chinese provinces, more than 90% of it is produced in just thirteen provinces, five of which (Shandong, Henan, Jiangsu, Hebei and Anhui) contribute more than 60% of the total production.[8]

Dr. Luigi Greco, a pediatrician from Naples University, wrote in 1995:

> *"Over the last 200 years of our modern age active genetic selection, and actual genetic manipulation, have changed the aspect of the original* Triticacee *enormously: from few grains and little gluten to great wheat harvests very enriched in gluten (50% of the protein content), well adapted to cultivation practices and ready to be handled by monstrous machinery".*[9]

He considers enriched wheat gluten the reason behind the higher celiac disease frequency, especially in populations whose genetic inheritance stems from ancient groups, which did not successfully adapt to tolerate this protein.

Chinese agriculture is also advancing towards a new era, and wheat gluten content is also higher than before. Therefore, the "absence" of celiac disease in China cannot be predicted based on wheat consumption. Since China is a multiracial country, HLA-DQ distribution differs according to area. Currently there are fifty-five ethnic minorities in China, which are officially recognized by the government, even when there are other groups that are still waiting to receive official recognition. Historical and genetic evidence suggest that many of them have been intermixing with the Han for many centuries[10] so that the phenotypical and genotypical differences between these groups and the mainstream Chinese population do not seem to be, in any case, significant. Besides, these groups add up, all told, to less than 10% of the total population.

More interesting seems to be the genetic frontier that exists between North and South China, within the Han ethnic group, as revealed by an article published in 2008 in the *European Journal of Human Genetics*.[11]

This difference would be consistent with the historical division between these regions, which, as explained before, has been determined by their bio-geographical conditions of both. The frequency of haplotype HLA-DQ2, DR3-DQ2 (HLA-DRB1*0301-DQA1*05-DQB1*02) is high in North China along the Old Silk Road, where wheat consumption is higher than in the south. The risk of having celiac disease can be higher, too. In the Jiansu province, the province where Dr. Wu and colleagues undertook their first investigation[12,13] the frequency of allele HLA-DQB1*0201/02 was 17.8%, HLA-DQB1*0302 was 5.6%, the frequency of haplotype HLA-DQA1 0501-DQB1 0201/02 (HLA -DQ2) was 7.2% and the frequency of haplotypes HLA-DQA1 0301/02/03-HLA-DQB1 0302 (HLA-DQ8) was 4.7%.[14]

Only a small fraction of the Caucasoid population which has inherited the HLA-DQ2 and/or HLA-DQ8 genes suffers from celiac disease and the contribution of the HLA region to the development of celiac disease among brothers is of 36%.[15] However, only a small percentage of HLA-DQ2 and DQ8 positive individuals actually develop the disease. Recent investigations using wide field genome suggest that genes in the MHC and non-MHC loci jointly contribute to the likelihood of the disease. Thus, a meta-analysis of the full genome linking studies has pointed out a contribution from the genes in the telomeric region in chromosome 10 (10q26.12-qter) and in chromosome 8 (8q22.2-q24.21).[16]

However, as pointed out by Kumar and colleagues, the recent and sizable amount of information that already exists needs further research in order to clarify its importance. These authors discuss and sum up the results of genetic studies in celiac disease, centering on non-HLA genes besides introducing new perspectives to identify the causal variants of the susceptibility loci in complex diseases like celiac disease and other associated autoimmune diseases, as well as possible mechanisms which could explain the pathogenesis of these diseases.[17] It should not be forgotten that the allele variations found in patients from a Caucasoid background will probably be different in Asian populations and that we must wait for similar studies from these regions.

3. Situation in Central America

There is no doubt regarding the date when wheat began to have an impact on the Central American population. There has been, since the nineteenth century, a whole slew of attempts (with varying degrees of credibility) of vindicating the idea of strong pre-Columbian contacts with the Old World, but, so far (even when the possibility of said contacts cannot be discarded beforehand), there is no evidence at all that suggests a formative or even a perceptible influence, from Old World sources, on the development of native American cultures.

There is relatively certain evidence that, around 1,000 AD, there were small Scandinavian settlements from Greenland on some of the islands just off the coasts in Northern Canada. These lands were known by the Scandinavians as *Vinland* and *Markland* and there are records that the Norsemen had frequent contacts with those whom they called *skrælings*,[18] that is to say, Native Americans (Inuit, the people who until recent decades were known as “eskimos”, or possibly members of other tribes).

However, to all intents and purposes, said contacts had no impact upon the ancestral cultural and subsistence patterns in the immediate region, much less on a continental scale.

In any case, the pre-Columbian diet was not only intrinsically gluten-free; it was also intrinsically free from any possibility of gluten cross-contamination, to boot. Additionally, the presence of human beings (*Homo sapiens*) in America dates from 13,000 years before the present and there is not, to date, evidence of any other kind of hominin in this continent. The most orthodox version regarding this fact argues that, near the end of the last ice age, the sea level was lower than it is today, so that there would have been a small strip of dry land where the Bering Strait is today.

Sometime during this period, according to this view, a small population or group of hunter-gatherers from Siberia would have migrated from the Old World towards what today is Alaska.

The members of this group, which is supposed to have been relatively homogenous genetically, would be the ultimate ancestors of all the native inhabitants of the New World.

This paradigm, however, known in archeology as "Clovis First" (based on the name of the eponymous paleoindian culture, the earliest and most archaic stage of American prehistory) is being strongly questioned since there is an ever-growing body of data which suggests the even earlier presence of humans in America, leading to the proposal of dates of 21,000 or even 40,000 years before the present for the peopling of the continent.[19]

Recent evidence, in fact, suggests a much more complex panorama than what was supposed before: A skeleton, known as the "Kennewick Man" (after the locale in Washington State, U.S.A., where it was found) was satisfactorily dated to a period between 7,300 and 7,600 B.C. Several anthropometric studies of its skull have yielded inconclusive results, but the evidence suggests that the cranial morphology of this individual has no exact parallels among known modern populations; in any case, he has more affinities with the Utari (the group formerly known as the Ainu) from North Japan or with the Polynesians than with typical native Americans.[20]

Something similar can be said of "Luzia", a female skeleton dating from about 9,500 B.C., found in the Vermelha cave near Belo Horizonte, Brazil. As with the Kennewick Man, cranial morphology analysis has yielded confusing results, of which the only thing that seems clear is that it differs substantially from the Siberian peoples who were the supposed sole ancestors of all Native Americans, up to the point where some have even classified its facial features as "negroid".[21]

This suggests that Native American populations have a much richer and complex genetic inheritance, and probably a much older one, than it had been supposed up until recent decades.

This panorama of phenotypical diversity is supported and made deeper by a study undertaken by a team headed by Dr. Antonio Torroni, from the University of Pavia, Italy[22,23] whose findings indicate that Native Americans descend from at least two genetically distinct groups. Another study recently published in *Nature* posits the existence of *three* very ancient migrations. These researchers, using a very high-resolution with 364,470 single-nucleotide polymorphisms have studied fifty-two Native American groups and seventeen Siberian groups.

They show that Native Americans descend from at least three Asian gene flows. Most descend from a single ancestral population, which they have named "First Americans", suggesting (according to some interpretations) that the initial population was followed by a southward expansion along the coast, with subsequent divisions but with little change in the gene flow after the divergence, above all in South America. The Chibchas seem to be an important exception on both sides of the Panama isthmus, since they possess ancestors from both North and South America.

To this panorama of inherent diversity in pre-Columbian Central America we can add the influx of European colonizers starting in the Sixteenth Century, who brought a very diverse genetic inheritance, the product of the complex history of their continent of origin.

The first wave of immigrants came mainly from the Iberian Peninsula and it includes a complex patchwork of peoples among which we can include (aside from the inheritance of the tribes that dwelt in it in pre-roman times, of uncertain relations) Iberians, Phoenicians, Romans, Basques, Greeks, Celts, Ostrogoths, Arabs, Berbers, etc.

To this, we must add the presence of large contingents of slaves forcibly brought from Africa, themselves, in turn, coming from various regions of this enormous continent, each of which possesses its own genetic diversity. Furthermore, to all this we must add the later arrival of groups, which hailed from other regions of Europe (Italy, Greece, etc.) or even Near Eastern groups, above all in the post-colonial period.

Clearly, it cannot be concluded that the mixing of peoples from the New World with peoples from the Old World could have easily foreseen genetic consequences, given the fact that we are talking about very large regions, each one of which, in turn, has a very complex genetic map.

When Spanish power collapsed in the New World, far from keeping any sort of cohesion, the diverse provinces of every Viceroyalty went, in a political and cultural sense, along their own separate ways, a fact that determined the way in which the descendants of recent immigrants and the descendants of Native Americans intermingled with each other. Due to this, neighboring Central American countries have clearly differentiated customs, habits, accents and even vocabulary.

Far from being a homogeneous region, Central America has a noteworthy genetic and cultural diversity that can affect the way CD manifests itself in each country and even within the different regions within each country, the social stratification imposed by Spanish administration and customs generated populations with different genetic compositions.

Figure 2. México and Guatemala; the only countries with significant wheat production

Currently, commercial influence from consumer patterns from the United States of America and Europe are being intensified by modern telecommunications networks and by recent free trade treaties. This influence includes an influx of great quantities of gluten-bearing industrial products.

This tendency has been developing for decades, particularly after the end (in the middle of the nineteen-eighties) of the internal military conflicts formerly endemic to the region. For this reason, it should not be unlikely that gluten may have already reached even the inhabitants of areas that are distant or at the margins of the commercial centers by means of medicines or food provided by welfare services or humanitarian organizations, or else by the growing penetration of affordable products in rural areas.

Even making tentative generalizations about the prevalence of celiac disease in this region would be inherently risky. Given the elevated number of variables that have been acting on the region, it is imperative to undertake properly designed epidemiologic and genetic studies. The prevalence may vary from one country to another, even from one region within a country to another. For example, in the highlands of Guatemala the ethnic composition of the population is markedly different from that of the larger cities. This is due to the fact that colonial cities tended to act as administrative centers, so that European-descended people would gather there, relegating the original inhabitants to rural areas.

Studies of genetic markers in these countries are practically non-existent. Confirmed celiac patients have been found in El Salvador by Dr. Mauricio Cromeyer with the cooperation of Ms. Karla María Zaldívar, MBA, PMP, of the *Asociación de Celíacos y Sensibles al Gluten de El Salvador* ("Celiac and Gluten Sensitive Patients' Association of El Salvador) ACELYSES and preliminary results are presented in Chapter 4 of this book.

4. Present and Future

Several environmental changes point to an increase of celiac disease in these regions. We can mentioned the deworming of rural populations which contribute to a change in the TH2 to TH1 predominant intestinal immune response, changes in the intestinal microbiota (mainly in urban areas due to access to antibiotics), changes in dietary habits due to the influence of "fast foods" and changes in traditional diets based on rice or maize due to the diffusion of diets with a higher gluten content.

5. Diagnostic Difficulties

It is necessary to analyze the difficulties in these countries regarding the identification of the disease as well as the techniques involved in its diagnosis. It is possible that general practitioners, specialists and pediatricians may not be familiar with this disease due to clinical heterogeneity of the disease and the low prevalence of the disease.

The main limitations of these studies lie in the absence of duodenal biopsies specimens, the lack of experience in optimizing the quantity and location of the biopsy samples as well as in a lack of

experience among the pathologists who analyze the samples. Every population where celiac disease is emerging needs to adjust its array of detection procedures to its particular conditions and needs.

Thus, in the aforementioned study by Wu and colleagues, seventy-three Han patients with irritable bowel syndrome with diarrhea (IBS-D) and five patients with insulin dependent diabetes mellitus were analyzed by serological tests. Six (7.7%) tested positive for antigliadin IgG antibodies (IgG AGA) and two (2.6%) tested positive for tissular transglutaminase IgA antibodies (tTG IgA)[12,13] in the Wuhan region. These initial data have been confirmed by a wider study in the region of Wuhan, which has only been published in abstract form. In this study, two hundred and eighty-two patients with irritable bowel syndrome with diarrhea and two hundred and ninety-six healthy controls underwent a combined serological test (QUANTA LiteTM h-tTG/DGP) which has, as antigen, human transglutaminase and deamidated peptides. Five patients with IBS tested positive for antibodies, as well as two healthy controls. The antibody levels were relatively low in comparison to what is reported from other countries.

6. Conclusion

Current sensitive and specific serological tests for celiac disease have allowed observing an increase of this disease's prevalence in several countries but the priority in emerging countries is the creation of interdisciplinary study groups, which will help to design specific protocols for each region.

6.1 Patients' Associations

Patients' associations in Central America are playing an important role in spreading knowledge about celiac disease. Besides ACELYSES, the *Asociación de Celíacos de Guatemala* ("Celiac Patients' Association of Guatemala") was founded in 2013 in that same country, by Dr.Estuardo Ligorría, who is deeply involved in the study of celiac disease and the treatment of local celiac patients. This association, which has just begun to hold meetings, has established communication with the relevant government institutions so as to secure a legal framework, which will benefit said patients.

In Panama, the *Fundación Celíacos de Panamá* ("Panama Celiac Patients' Foundation", FUCEPA) is also striving to help local celiac patients and their families by means of the dissemination of information, which will improve these patients' quality of life; it has also, among its aims, the improvement of medical criteria and diagnostic procedures, as well as the passing of laws regarding the labelling of products regarding their gluten content.

In Costa Rica, the *Asociación Pro-Personas Celíacas* ("Pro Celiac Persons' Association", APPCEL), founded in 2004, has worked towards the same ends, offering psychological support as well as useful information by means of an electronic newsletter and has been involved in changing this country's laws so that celiac patients may have access to safe food and properly labelled products.

The *Centro de Información sobre la Enfermedad Celíaca* ("Celiac Disease Information Center", CIEC), founded by Ms. Amavilia Pérez Villavicencio, MSc, has its headquarters also in Costa Rica. In Honduras and Nicaragua there is still very little information available to the general population, but in these countries efforts are being made, by some of their gastroenterologists, whose interest has been aroused by recent developments in the field, to better understand this disease and to lessen its impact on the population and on their countries' health care systems.

Acknowledgements

We would like to acknowledge the work of our colleagues in China, Dr. Wu Jing (Digestive Disease Department, *Jiangsu Provincial Hospital of Traditional Chinese Medicine*, Nanjing, Jiangsu Province, P.R. China) and Prof. Xia Bing (Director of Department of Gastroenterology, Chair of Department of Internal Medicine Zhongnan Hospital, Wuhan University School of Medicine, Wuhan, Hubei, P.R. China).

In Central America we are grateful to Dr. Mauricio Cromeyer (*Hospital de Diagnóstico Escalón*, Villavicencio Plaza, Paseo General Escalón, Colonia Escalón, San Salvador, El Salvador C.A.) and Ms. Karla María Zaldívar, MBA, PMP., (San Salvador, El Salvador, C.A.) for the enthusiasm with which they dedicate themselves to the study of celiac disease and provided interesting data.

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