THE IMPORTANCE OF THE MULTIDISCIPLINARY APPROACH TO DEAL WITH THE NEW EPIDEMIOLOGICAL SCENARIO OF CHAGAS DISEASE (GLOBAL HEALTH).

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ABSTRACT

There are currently two major factors that have modified the epidemiology of Chagas disease in the last decades: climate change and migration flows. In this new scenario, there are new challenges to control and prevent *T. cruzi* infection in endemic countries, such as the control of a wider distribution of triatomine vectors or the reinforcement of vertical transmission programs.. In non-endemic areas, few countries are aware of the emergence of this new disease and have established changes in their health systems. To address this new public health challenge, the priorities should be control programs to avoid new cases of *T. cruzi* infection acquired through vertical transmission, blood transfusion or organ transplant.

In both, endemic and non-endemic areas, the international community and all the actors involved in Chagas disease must join efforts mainly in two directions: better management of the infection in affected individuals and more research to cover the knowledge gap mainly in physiopathology, diagnosis and treatment.

KEYWORDS: Chagas disease, *Trypanosoma cruzi*, *Triatoma infestans*, migration, oral transmission, benznidazole.

1.- Introduction: the keys of disease globalization in the XXI century

Chagas disease, caused by *Trypanosoma cruzi* parasite, was originally described as an endemic disease focused in populations living in poor rural areas of Latin American countries.

From the ecological point of view, there have been two major factors that have modified the epidemiology of the disease: climate change and human migration. Even if it is difficult to quantify the impact of climate change in vector borne disease transmission, altitude levels of the traditionally defined endemic areas , the wild cycle of triatomine and the vector-parasite interaction can be modified due to global warming.[1,2]

Moreover, anthropical factor, through various initiatives of vector control, add an important element to the epidemiological issue in endemic countries.

Historically, migration has been the key factor in the dissemination of Chagas disease [3]. Recently, migrant flows have brought infected individuals to Latin American urban areas and beyond the borders of Latin America, changing the epidemiology of the disease [4].

The migratory flows between Latin American and European countries are not new. During the fifteenth century many European citizens migrated towards the Americas. This process continued until the fifties of the twentieth century, when Latin America became a region of origin of international migrants, being the United States and Europe the main receptors of Latin America migrants. This trend has continued until 2008, when due to the economic crisis the migratory flows from LA significantly decreased. United States is the main destination of Latin American migration with approximately 20.5 million Latin American immigrants living in the country, according

to some estimates.[5] Today, around 3.5 million people from Latin American live in Europe.[6] In Europe, the distribution by country of Lain American migrants follows a patchy pattern, where certain few countries concentrate most of the Latin American migration. Spain, with over half of these migrants, is undoubtedly the most important recipient, followed by Italy, France, and United Kingdom.[7]

This initial distribution is changing due to the economic crisis and currently there is a redistribution of Latin American migration, especially from Spain to other European countries. [6]

One of the features that affect many Latin American immigrants today is the fact that the migration process does not stop with a single shift; quite often migrants look for job opportunities in three or more countries in relatively short periods of time. These frequent changes involve European and American countries, posing a challenge to the health care of these people.

2.- New characteristics of Chagas disease in endemic countries

Trypanosoma cruzi infection is a complex entity caused by a heterogeneous species of the parasite (*T. cruzi*) that implies a wide diversity of animals in the wild cycle, playing domestic animals an important epidemiological role in some areas.[8] The distribution of Chagas disease in endemic areas has been described as patchy and heterogeneous, involving different ecological niches and more than one hundred triatominae species, the vector of the disease.[9] Five triatomine vectors species (*T. infestans, R. prolixus, T. dimidiata, P. megistus, and T. brasiliensis*) have a major epidemiological importance,[10] and it seems that there is a close association between some triatomine vector species and some specific strains of *T.cruzi*.[11,12]

The transmission of *T. cruzi* in humans can occur in in well-known ways, and several approaches of control have been developed.

Vector transmission and programs of vector control

The implementation of vector control programs started in the 90's through several initiatives along the endemic countries has contributed to change dramatically the epidemiology of Chagas disease in Latin America.[13,14] The goal in most of these programs was the interruption of the domestic and peridomestic cycles of transmission through insecticide spraying. These programs - only useful for domiciliary vectors - have been successful in several countries: Brazil, Uruguay and Chile have been declared free from disease transmission by *T.infestans*, as well as specific departments of several other countries. [15,16] Equally, Guatemala was certified as being free from disease transmission by *Rhodnius prolixus*, the main domiciliated vector for Chagas disease in Central America.[16] But the temporal action of insecticides is not permanent. As demonstrated by some authors, recolonisation of houses by sylvatic triatomine populations may explain some difficulties encountered in vector control.[17]

Triatomine re-infestation is one of the major challenges in endemic areas, which oblige to maintain active the vector control programs. The decentralization of vector control is still controversial, although it is one of the keys for a sustainable entomological surveillance. Selective control and surveillance strategies are required due to the risk of possible domiciliary re-infestations.[16]

Moreover, there are reports showing the emergence of insecticide resistance among triatominos.[18,19]

Rural to urban migration

In endemic countries, and mainly due to economic reasons, people living in rural areas moved to urban areas, increasing urbanization in periurban areas with poor hygienic conditions and where *T.cruzi* transmission can persist.[20]

Increasing detection of *T. cruzi* infection cases transmitted by oral transmission

Human oral infection is caused by ingestion of drinks or food contaminated with infected triatomine bugs or their feces. It has been rarely described up to now, but in the last years there has been an increase of new cases and outbreaks reported, mainly in wild environments [21] but also in urban areas. Several cases and outbreaks have been reported in Brazil, Venezuela, Colombia, Mexico, Argentina and Bolivia. [22-26]

Vertical transmission: the lack of surveillance programs

Vertical transmission of Chagas disease is one the main challenges of health in endemic countries,[27,28] and it is not well managed yet. Due to the success of the programs of vector and blood bank control, congenital transmission has obtained increasing epidemiological importance.[29] Rates of congenital *T.cruzi* transmission range from 0%-28.6%,[30] and the WHO estimated number of new cases of congenital *T. cruzi* infection is around 8.668 cases per year. [31]

Successful blood banks control in Latin America countries

Specific screening for *T. cruzi* in blood banks has been improved successfully in all Latin-American countries in the last years, with a coverage close to 100% [32,33]

3.- Chagas as emerging disease in non-endemic countries

As mentioned before, in non-endemic countries new migration flows have been the key for the emergence of Chagas disease in areas where it was not previously

present. The importance of Chagas disease in this new scenario is directly related to the volume of migration flows received by each host country and also related to the specific origin of migrants received, since the distribution of Chagas disease is not homogeneous within endemic countries.

Europe and the United States have been the main recipients of Latin-American migration [3,33], and due to the current economic crisis some trends of migrant dispersion among European countries have been detected.

It is estimated that in Europe there are between 68.000 and 123.000 infected people with *T. cruzi*, most of them living in Spain. However, until 2009 only 4.290 cases have been reported. [4,35]

In the United States, based on population figures from countries where Chagas disease is endemic, it is estimated that in 2011 there were about 300.000 people infected with *T.cruzi.*[34]

In other countries with Latin American migration (Canada, Japan, Australia, other European countries) the number of people infected by *T. cruzi* ranges from 140 (Austria) to over 12000 (England).[4,35,36]

In non-endemic countries *T.cruzi* transmission occurs through blood transfusion and organ transplants from infected donors and from infected mothers to their children as well.

Blood banks control strategies in non-endemic countries

Few studies have been conducted in blood banks in non-endemic countries to assess the risk of transmission in blood banks. In Spain, one study showed that 0.62% of the Latin American donors (N= 1172) were positive for Chagas disease, but the percentage increased (10%) when only Bolivian migrants were considered.[37] In

other studies between 1% and 5% of blood donors were detected to be positive for Chagas disease in the U.S., Canada and Germany [38-40]

Additionally, several cases of Chagas disease transmission in blood and transplants recipients have been reported in Europe and the United States [41-46] In Spain, universal blood donation screening for *T. cruzi* began in 2005 and in the U.S. in 2007. In Europe only four more countries (France, Switzerland, United Kingdom and Sweden) have implemented effective measures to control risk of Chagas disease infection via blood transfusion.[47-49]

A "new" route of transmission: organ transplantation

Organ transplantation is more frequent in non-endemic than in endemic countries, and the new era of organ transplantation has opened another route of transmission of the parasite. The management of this clinical condition is especially important while immunosuppression is mandatory in the context of organ transplant. Several guidelines in endemic and non-endemic countries have been published for this new scenario.[50,52]

Non-endemic countries becoming "endemic" countries: vertical transmission

The risk of mother-to-child transmission is of concern in non-endemic countries. In a study performed in Spain, the rate of prevalence of *T. cruzi* in Latin American pregnant women (N= 1350) was 3.4% (27% in Bolivian mothers), with 7.3% of infected newborns.[53]

In Europe and the United States, respectively, it is estimated that each year between 20 to 183, and 63 to 115 of newborns are infected with *T. cruzi* [33,34]. In fact, several cases of vertical transmission have already been identified in Europe.[53-59]

In Spain, a study showed that doing a screening in pregnant women for early detection and treatment to children infected by *T. cruzi* was cost-effective.[60]

Following epidemiological and economic data, some regions of European countries, particularly Catalonia, Valencia, Galicia and more recently Andalucía (Spain) and Tuscany (Italy) have already approved official control measures in pregnant women at risk of *T.cruzi* infection and the early control of newborns from Chagas positive mothers.[61-63]

Also in Europe, there are some other punctual initiatives from some centers for the control of newborns whose mothers are infected with *T. cruzi*. [49] Due to the high efficacy of specific *T. cruzi* treatment in newborns (of nearly 100%), programs for the control of Chagas disease via congenital transmission should be implemented in all countries to screen pregnant women coming from endemic areas with the objective of early treating the infected newborns.

4.- Challenges on Chagas disease management in this new global scenario.

Despite being globalized, Chagas disease remains one of the 17 neglected tropical diseases declared by the World Health Organization. Chagas disease has a significant economic impact. The global costs for Chagas disease have been estimated in $7.19 billion per year, similar or even higher to those of other important diseases. [64]

Vector control programs and oral transmission of Chagas disease are specific challenges for endemic countries, although due to human migration the repercussion of the success or failure of such programs goes beyond the Americas. Although endemic

countries have direct responsibility for maintaining appropriate vector control programs, strengthening such programs is a major global challenge in which international community should be involved.

Other challenges on Chagas disease are universal, mainly to improve control programs of vertical transmission in endemic areas, and to develop such programs in non-endemic countries. Endemic and many of the newly affected countries are registering cases of the disease transmitted congenitally. However, few countries are aware of the emergence of this new disease and few have established changes in their health system to address this new challenge for public health.[49] Despite the clinical, economic and epidemiological data available, effective vertical transmission control programs are not in place both in most endemic and non-endemic countries. [49]

As a neglected disease, there are several gaps in the knowledge of crucial points in Chagas disease: the life cycle of *T.cruzi* in human hosts, the ecology of sylvatic cycle, the mechanisms of action of drugs against the parasite and the keys to improve the accessibility of the patients to the health systems. Funding for Chagas disease in 2012 was 31.7 US$ million, which represents around 1% of total R&D funding spent on neglected diseases globally.[65]

In this scenario, care of people with Chagas disease has been hampered by several factors. Here, we want to highlight some of them: the adverse events caused by the only two useful drugs against *T. cruzi*, the lack of early biomarkers of therapeutic efficacy and, above all, the importance given to the autoimmune theory of the disease that has prevailed for many years. For years, health professionals have been trained in the belief that Chagas disease had no treatment and in the fear of giving the specific treatment due to the high rates of adverse events. Other consequences of the lack of medical care are

that patients carry the social stigma and negative psychological and economic effects of having an incurable disease.

"The economic effects and the complexity of medical care are most evident in the more advanced stages of the disease (pacemakers, defibrillators, colon surgery ...) , and in these cases it is not always possible to give the required care , either by economic or geographical reasons".

Moreover, research for new and better drugs have been slowed or forgotten for years until very recently.[66]

In non-endemic countries, there are other important factors relating to the care of people affected. One of them is the lack of knowledge about the disease of many health professionals. This is aggravated by the change of migration patterns within or between countries when migrants are forced to move in search of better job opportunities and also for the wide diversity and poor specificity of symptoms of Chagas disease. Another problem relates to the policies of some governments to restrict the access of immigrants to health systems. .[6]

In order to overcome these limitations in patients' treatment, it is important to consider that: a) adverse events of antiparasitic drugs against *T.cruzi* are frequent. Even most of them are minor, a considerable percentage of treated patients suffer from adverse events and there is a need for monitoring patients closely during the treatment;[67,68] b) antiparasitic treatment provided to young women prevent further cases of congenital Chagas disease;[69] c) benznidazole induce a persistent negativization of the peripheral parasitemia in around 80% of treated patients 12 months after treatment.[70-72]; d) even if evidences with good clinical outcomes are lacking, there is a clinical benefit in treating patients .[73] ; e) the training of health professionals is vital for good patient care; f) to integrate the care of patients with Chagas disease into the primary health programs is probably the most effective strategy in both, endemic and non-endemic countries.

5.- Conclusions.

The confluence of a disease influenced by changes in ecology and epidemiology, with a long asymptomatic phase, not clearly perceived as being related to infection, and affecting marginalized populations, has resulted in a silent public health crisis. [74]

For facing this challenging disease, the international community and all the actors that play a role against Chagas disease must join efforts. There are precedents, such as the success of vector control programs, which indicate that when various actors come together to arrange a common and clear goal, this can be achieved. [75]

In fact, a multidisciplinary approach is essential to address a health problem that is multifaceted, which includes the coordination of various control programs (vector , vertical , blood banks , transplant), and the attention to affected people (primary care, different specialists) . Moreover, the decision makers must decide priorities within their competence in face of other health problems and coordinate with professionals working in the field and with the people affected.

In 2012, a community of international partners endorsed the London Declaration on Neglected Tropical Diseases (NTDs).[76] This initiative, which calls to coordinate efforts to eliminate or control 10 NTDs, including Chagas disease, drew a new scenario of possibilities until 2020. However, few years after the initiative it seems that little have been done and that the defined goals need to be revised.[77]

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