Es un honor para mí, presidir esta Conferencia de Chagas Congénito a cargo de un experto de la jerarquía de la Dra. Myriam Lorca, que la tituló "Congenital Chagas' disease in Chile: Incidence, Diagnosis and treatment evaluation by PCR".

La misma lleva el nombre de Machado-Guerreiro en Homenaje a los creadores de la reacción de fijación de complemento, que se usó durante tanto tiempo en el diagnóstico de la Enfermedad de Chagas crónico.

Una de las formas reconocidas en la actualidad de transmisión de la enfermedad de Chagas, es la connatal que ya en los primeros años fue registrada por Carlos Chagas.

Es conocida la importancia de establecer el diagnóstico precoz de ésta, ya que permite instaurar el tratamiento inmediato, obteniendo altos índices de curación de los pacientes. También conocemos que las estimaciones existentes de esta nosología, que son pocas, varían entre un 0,5 al 6 % para los hijos de madres chagásicas de áreas endémicas y no endémicas.

Es importante resaltar y reiterar que para establecer el diagnóstico de Chagas Congénito es necesario conocer su existencia, que aún hoy día, no es tenida en cuenta en muchos servicios de obstetricia y la investigación de la madre y el niño.

De allí la importancia del aporte que la Dra. Lorca nos brindará.

Dra. Luisa Gimenez
Encargada del Sector Chagas
Servicio de Cardiología del Hospital Alvarez
Buenos Aires, Argentina.
Congenital Chagas' disease is produced after passage of *Trypanosoma. cruzi* from the infected mother to the fetus via the placenta. (1)

Since the disease through the vector has been practically eliminated in Chile and others countries in Latin America, we have been considered important to examine certain aspects of this mechanism of infection which should be taking in account in futures programs of intervention in the transmission of the parasite to the human beans

**EPIDEMIOLOGY OF THE DISEASE**

The prevalence of Chagas' disease in pregnant women ranges from 8% (Uruguay) to 50% (Bolivia), the last studies conducted in Argentina have demonstrated a 9% of the maternal infection and in Paraguay 7.7 to 10.5%. (1,2,3)In Chile the infection level reported ranges from 1 to 10% in women at reproductive age; however prevalence of 20% were diagnosed in several regions of the country (4-7).

The incidence of the congenital infection ranges according the different studies conducted in Latin America between1,9 and 10% (2,3,4,5)

**CLINICAL ASPECTS**

The infection by *T. cruzi* follows different patterns when compared to toxoplasmosis. The infection of the fetus may occur at any time of the gestation (acute or chronic), it may infect the fetus in a second opportunity, or twins at the same time. The infection may produce pathology in the growing fetus but usually not abortion. However in HIV infected woman with Chagas' disease infection the abortion has been demonstrated (8).

At birth, the child may show a broad spectrum of clinical manifestations, ranging from asymptomatic to acute syndrome that could be fatal. Approximately 80% of infected mother may not transmit the parasite to the fetus during gestation, and will give birth a healthy child. Ten to 20% of the cases, *T. cruzi* will cross the placenta and infect the fetus (9). The consequences of the infection on the newborn child will depend upon the time of infection, resulting in the birth of asymtomatic or symptomatic infected and inclusively a death child.

In the case of infected child the outcome of the disease will determine the future of the child: cure, chronic Chagas' disease or death are some of the possibilities. Several studies conducted in mother-child have been realized in several regions of Chile, including areas with high and low prevalence of the disease. In the areas with high frequency the number of positive cases ranger from 2.4 to 26.5% in pregnant women (4-7). In those areas with low frequency, the prevalence is usually between 1 to 2%. However the transmission in both areas reaches from 13 to 22 % (10). Approximately 80% of the children born to infected mothers will be asymptomatic and normal. In the case of symptomatic infected child, they will show low body weight at birth, ictericia, anemia, hepato-splenomegaly, meningoencephalitis, myocarditis,
and ocular lesions. In extreme cases death may occur.

The early diagnosis of the infection has the advantage to allow opportune treatment, which will prevent further lesions. When the treatment start before six months of age, the child will recover from the symptoms and the parasites will be eliminated from the organism. This outcome has been confirmed in patients observed for four years after the completion of the treatment. In cases treated after two years of age (post-infection), the child developed cardiopathy, megacolon and neurologic symptoms (11-12). The factors that influence the transmission of the infection from mother to fetus have not been clearly identified. Several questions have been formulated, and the answer may require extensive investigation:

Are there several \textit{T. cruzi} strains infecting the population or is it due to characteristics of the pregnant women, during particular period of gestation that may favor the extreme variation in the infection rates of the fetus?

Are the differences of prevalence in the different regions due to the presence of several \textit{T. cruzi} strains?

The variability of the clinical manifestations of the disease is due several \textit{T. cruzi} strains?

Studies conducted in Chile during 1980 showed that transplacental infection in the general population was less than 3% in the regions with high exposure to the parasite and the vector. However in the regions with low exposure level, the rate of infection was higher (10%) in the same group of people (Table 1). These differences were considered the result of the use of different methodologies to evaluate the disease frequency or an acquired infection by the vector in the high endemic area. Recent studies (13) have demonstrated that the risk of infection has been reduced to a minimum due to effective elimination of the vector in those areas with high risk.

<table>
<thead>
<tr>
<th>Year</th>
<th>Author</th>
<th>Chagasic Endemic area</th>
<th>Pregnant woman N° %</th>
<th>% Congenital transmission</th>
</tr>
</thead>
<tbody>
<tr>
<td>1990</td>
<td>Muñoz et al</td>
<td>High</td>
<td>547 26.5</td>
<td>2.1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Low</td>
<td>4,237 1.2</td>
<td>9.8</td>
</tr>
<tr>
<td>1997</td>
<td>Bahamonde et al</td>
<td>High</td>
<td>1,667 2.4</td>
<td>12.5</td>
</tr>
<tr>
<td>2000</td>
<td>Garcia et al</td>
<td>High</td>
<td>938 7.8</td>
<td>16.4</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Low</td>
<td>5,495 1.4</td>
<td>28.2</td>
</tr>
</tbody>
</table>

**Table 1**

\textit{Trypanosoma cruzi} infection in pregnant women in Chile, evolution of the prevalence of the maternal infection and the incidence of congenital transmission in endemic areas of Chile

**MOLECULAR ASPECTS**

Several reports indicate the existence of \textit{T. cruzi} strains in Latin America. The identification has been done using zymodemes, schizodemes and recently PCR-RFLP, PCR and hybridization with specific radionucleotid probe against clonets of \textit{T. cruzi}.

Initial work that was conducted revealed the existence of distinct selvatic and wild \textit{T. cruzi} strains. Currently it has been determined that certain strains show preference for nervous tissues over other organs. Genetic studies of \textit{T. cruzi} suggest that there are isolates that show variation in the level of virulence to the host (14-18).

Three main clonets have been differentiated up to this moment. Clonet 19/20 produce mainly encephalitis, infect striated muscle and only a 20% of the cardiac tissue, show also a high prevalence in the vector and low frequency in humans beans. On the other side clonet 39 infect specially striated muscle and mainly (83%) cardiac tissue and liver and spleen cells. This clonet also show a high frequency in human beans and a medium prevalence in the vector.
Congenital infection by *T. cruzi* has been extensively studied in Chile to determine the genetic background of the parasite as well as the possible influence on the consequences of a chronic infection or the evolution after the treatment. The results of the genetic background of the strains, which infected congenitally child, are showed in table 3. According the results the main clonet present in congenital cases in Chile is Clonet 39 in high and low endemic area. The clonet 19/20 is less frequent and is present only in low endemic area (3 cases). This result could explain some of the differences in the frequency the transmission in both areas. There are not relationship between the clonets and the clinical form of presentation of the congenital cases. Moreover all the studied cases (21) have been asymptomatic.

### Table 2

<table>
<thead>
<tr>
<th>Cases N°</th>
<th>Procedence</th>
<th>Congenital transmission</th>
<th>Clonet 39</th>
<th>Clonet 19/20</th>
</tr>
</thead>
<tbody>
<tr>
<td>12</td>
<td>High Endemia</td>
<td>16.4</td>
<td>12</td>
<td>0</td>
</tr>
<tr>
<td>9</td>
<td>Low Endemia</td>
<td>28.2</td>
<td>6</td>
<td>3</td>
</tr>
</tbody>
</table>

### DIAGNOSIS

Two methods are used to diagnose *T. cruzi* infection: Direct and indirect or serologic techniques. (9)

- **Direct methods** are used in newborn to confirm connate infection, including microstout and xenodiagnosis. Both methods are based on concentration of parasites in the blood. They show low yield particularly in asymptomatic cases with low parasitemia. The use of PCR has facilitated the diagnosis and increased the sensitivity by 97%, independent of the type of infection (3,19-23) (Table 2)

### Table 3

**Trypanosoma cruzi**: PCR results in children born from infected mothers

<table>
<thead>
<tr>
<th>N° + Mothers</th>
<th>Endemic Area</th>
<th>PCR NB N° + %</th>
<th>Xeno + %</th>
<th>IgG Serology at birth N° %</th>
<th>IgG Serology 6month N° %</th>
<th>Clinical Manifestation Asym. Sym</th>
</tr>
</thead>
<tbody>
<tr>
<td>73 High</td>
<td>73 12 16,4</td>
<td>1 1,4</td>
<td>73 100</td>
<td>5 6,3</td>
<td>12 0</td>
<td></td>
</tr>
<tr>
<td>78 Low</td>
<td>78 22 28,2</td>
<td>3 3,9</td>
<td>78 100</td>
<td>N/D</td>
<td>22 0</td>
<td></td>
</tr>
<tr>
<td></td>
<td>151 22,5</td>
<td>4 2,6</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- **Indirect or serologic methods** include ELISA and immunofluorescence methods. They allow the detection of IgG, IgM, and IgA antibodies to the parasite (10, 11). The presence of IgG to *T. cruzi* in the blood of a newborn does not indicate neonatal infection unless the titers are 2 titer higher those measured in the mother and they persist for 6 months after birth. Recently developed methods using recombinant or synthetic antigens allowed a better characterization of neonatal Chagas’ disease.(24-25)

Congenital infection is confirmed by the finding the protozoa using direct methods. In addition, serologic methods will show significant levels of IgG and IgM. IgG titers should be at least 2 titers over the maternal levels for at least six months after birth. Before the initiation of treatment, it is recommended to conduct the following general tests: Hemogram, liver function, glycemia, electrocardiogram, echocardiogram and brain echogram. In addition, it is suggested to examine retina, determine protein content in spinal fluid, together with bacteria culture, and *T. cruzi* IgG determination using ELISA or immunofluorescence techniques. Nutritional status of the patient should also be evaluated before the initiation of the treatment.

### TREATMENT

Current the treatment during the acute stage involves the use of niturtimox for up to 60 days using incrementing dosages. The patients should be monitored using clinical examination every 15 days to determine adverse effects and conduct blood and liver function diagnostic tests. In addition, the patient should be evaluated for antibodies against *T. cruzi* using ELISA or immunofluorescence tests, PCR and xenodiagnosis after 1, 6, 12, 24 and 36 months after the treatment period. Most of the cases, it is possible to obtain complete cure of the disease and negative results in parasitological diagnosis. The most frequent adverse reactions observed include hypersensitivity, gastrointestinal symptoms, peripheral nervous symptoms and convulsions that respond to Phenobarbital medication. In children born from infected mothers that show evidences of *T. cruzi* infection, it is considered to be a transplacental infection.
and should receive treatment.(4)

**SURVEILLANCE AND INTERVENTION PROGRAM**

The program will target transplacental transmission diagnosis in mother and newborn child, followed by treatment if needed, close control of positive cases for a year after medication, epidemiological study of the family and report to the National Health Service. Medical treatment should not be initiated in pregnant or lactating women. It is recommended for women living in an area with high Chagas’ disease risk to undergo medical evaluation, treatment if needed, sanitary education and antibody study of the immediate family.

**CONCLUSIONS**

1. The success in the control of vector transmitted Chagas’ disease and screening programs in blood banks in the reduction of the frequency of human cases, has uncovered the Public Health importance of transplacental transmission of *T. cruzi*.

2. The early diagnosis of the infection and the adequate treatment result in The serological, clinical and parasitological cure of the infection in the Newborn.

3. PCR have been demonstrated to be an excellent method of the diagnosis of congenital Chagas disease with high sensitivity and specificity.

4. Two main clonets of *Trypanosoma cruzi* are present in the infected child and associated with the transmission and the geographical procedence.

5. Up to this moment there are not evidence of relationship between the clone and the clinical manifestation of the infection.

6. The cost of surveillance and intervention program is lower than the medical treatment required for chronic Chagas’ disease cases.

7. Early treatment of *T. cruzi* infected children will produce complete cure and interruption of the cycle.

8. In countries where other surveillance and intervention programs for mother and child are in place, the inclusion of Chagas’ disease monitoring will maximize the impact of the activities that target this segment of the population.

**REFERENCES**


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