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EDITORIAL

Challenges and opportunities in the vertical transmission of Chagas disease☆

Luces y sombras en la transmisión vertical de la enfermedad de Chagas

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Since the second half of the XX century, the measures implemented in endemic countries to control Chagas disease (CD) have succeeded in reducing its incidence. Nevertheless, there are still regions where vector-borne transmission endures (Bolivia, Paraguay, Mexico, etc.) and therefore new cases of infection occur in the younger population. The WHO estimates that there are about 10 million individuals with CD worldwide.[1] Although there have been improvements in the diagnosis and management of these patients, pharmacological treatment continues to be suboptimal and is not free of toxicity. Furthermore, early diagnosis is difficult, which is in part due to the absence of standardised screening and management programmes even within each country.

Due to the effects of campaigns to control the disease in endemic regions and the influence of migration patterns, vertical transmission now accounts for 22% of all new infections. It is estimated that more than 8000 children are born each year with infection by *Trypanosoma cruzi*, and addressing this mode of transmission is key to achieve control of this disease in Latin America and beyond.

In Europe, Spain is the country with the highest number of individuals with CD, and reported cases most frequently correspond to individuals of Bolivian ancestry, who amount to 81% of the total. It is estimated that 50 000 people are infected in Spain. Of these, 60% are women of childbearing age, which poses a risk of infection outside endemic regions through vertical transmission (VT). However, the disease is still underdiagnosed, with some studies reporting that 90% of cases are undetected. Some of the reasons for this are socio-cultural or involve the beliefs of patients themselves, which hinders early diagnosis when patients are still asymptomatic, and therefore early treatment. Thus, some patients who receive the diagnosis in the receiving country had actually received the diagnosis in their country of origin, although it was not followed by treatment.[2] Screening for CD is often part of routine checkups, especially during pregnancy or before blood donation. In this regard, adequate training of health care professionals allowing them to counsel and guide patients at risk of CD is essential to avoid gaps in the detection of CD and missed opportunities for diagnosis and treatment.

At present, Spain has protocols for screening blood and organ donors. There are also protocols for screening pregnant women from endemic regions. However, screening

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is only universal in some autonomous communities, such as Murcia, Valencia, Galicia and Catalonia. There is a working group on CD in the Community of Madrid that is developing several initiatives and seeking the collaboration of the pertinent institutions to achieve universal screening in pregnant women at risk, as at present screening in most centres mainly targets mothers from Bolivia, where the prevalence is higher (of nearly 18%) (https://www.smmc.es/chagas). Thus, for example, a study recently published by Francisco-Gonzalez et al. in which 1244 Latin American pregnant women between 2013 and 2015 were screened for CD, 40 had the disease, of who 85% were from Bolivia. The prevalence was 3.2% (95% confidence interval [CI], 2.4%–4.4%), with 1 case of vertical transmission, corresponding to a proportion of VT of 2.8% of the total (95% CI, 0%–15%).[3]

This aspect is of vital importance, as on one hand testing pregnant women and newborns allows the early diagnosis and treatment of offspring in cases of vertical transmission, with treatment in this age group being nearly 100% effective with fewer side effects. On the other hand, early treatment of women of childbearing age with CD is not only beneficial to women themselves, but has the advantage of reducing the incidence of mother-to-child vertical transmission, as evinced by several authors. Pregnant women are more likely to have positive PCR results compared to non-pregnant women, which may be due to the relative immunosuppression that takes place during pregnancy. On the other hand, a positive result of PCR assay on a blood sample (which is related to the level of parasitaemia) is associated with an increased risk of VT. In this regard, the prospective study by Murcia et al. in 159 women, 38 of whom were treated before pregnancy, found significant differences in the rate of VT based on whether mothers had or not been treated (13% vs 0%, respectively). A separate analysis of mothers who had been treated before pregnancy found that the PCR assay conducted during pregnancy had been negative in 92% compared to 32% of those who had not been treated. Furthermore, the rate of VT in mothers with negative PCR results was zero (0 infected children/74 mothers vs 16 children with CD/85 women with positive PCR during pregnancy). Thus, women with negative PCR results did not transmit the infection, so that the negative predictive value of PCR was 100%, although the positive predictive value was 18.8%.[4] For all of the above, it would make sense to include PCR in the evaluation of pregnant women with CD, as negative results are indicative of a low risk of VT.

Another aspect to consider is the need to improve the diagnostic algorithm for newborns of mothers with CD. At present, performance of a microhaematocrit is still recommended in newborns, as it allows the visualisation of the parasite, which is definitive proof of infection, although it is well known that its performance is not always optimal. Due to the complexity of the technique, its results depend on the experience of the individual performing the test and the time elapsed from sample collection to processing, so that its overall sensitivity is less than 50%. As a result, the use of PCR followed by serological confirmation at 9 months is gradually becoming the gold standard for perinatal diagnosis. There are still limitations, such as the potential for false PCR positives at birth due to contamination with maternal blood, which requires confirmation with testing of another sample collected at a later time, or the variability in the sensitivity of the method based on the technique used, the staff performing the test, etc. In our study, the sensitivity of PCR was high, even with low levels of parasitaemia, although collection of several samples was still required to optimise diagnosis. Along these lines, a study in 38 infected children performed by Messenger et al. found that the sensitivity increased with the combination of 2 PCR assays on samples collected at birth and 1 month of life (84.2% for the combination vs 66%–76% for isolated measurements at birth or 1 month of life), while the specificity was high for all options ($\geq$97%).[5] On the other hand, symptomatic children are more likely to have positive results, as they have higher levels of parasitaemia, although the proportion of symptomatic patients has dropped in recent years, probably due to improvements in prenatal care. Furthermore, PCR allows the assessment of treatment efficacy. Lastly, there are other limitations, such as the need to confirm the disappearance of maternal antibodies at around 9 months of age. This is hindered by significant losses to follow up, estimated at more than 20% of children, in whom a final diagnosis is thus not made. Therefore, the diagnostic algorithm probably based on PCR techniques still needs improvement.

Last of all, the cornerstone of CD control is the improvement of treatment. It is of utmost importance that we develop more effective and easily tolerated drugs. Nevertheless, the effectiveness and tolerability of currently available drugs is greater in children than in adults (in adults in the chronic phase of disease, the efficacy is around 7%–8% in some studies whereas the cure rate in children aged less than 14 years is 85.7%).

When it comes to the therapeutic armamentarium against CD, there are two major drugs: nifurtimox (NFX), which was the first drug used but whose side effects relegated it to second place, and benznidazole (BNZ), which exhibits an excellent parasiticidal activity in the acute phase of disease, as observed in infants aged less than 1 year, but is less effective in the chronic phase (80% vs 8%).[6] Recently, the BENEFIT trial (double-blind trial of BNZ in patients with chronic Chagas cardiomyopathy) demonstrated that BNZ significantly reduced serum parasite detection but did not significantly reduce cardiac clinical deterioration. However, a recent retrospective study showed that BNZ prevented the development of electrocardiographic abnormalities, although the sample included patients in earlier stages of disease with normal electrocardiographic patterns.[7] We await the results of the CHICAMOCHA 3 NFX trial, which have yet to be published.

Until recently, the only dosage forms available for the paediatric population consisted of tablets containing 50 or 100 mg of BNZ (Laboratorio ELEA), which led to the use of compounded preparations and home-made mixtures. In Brazil, LAFEPE developed a 12.5 mg tablet for children weighing less than 20 kg, which has proven efficacious in eliminating the parasites. This paediatric formulation was licensed in Brazil in 2011 and included in the WHO model list of essential medicines for children in 2013, although it is still unavailable in many countries, including Spain, where only 100 mg tablets are available. Another important aspect that has emerged in recent years is evidence that lower doses of BNZ (BERENICE study, http://www.berenice-project.eu/index.php?lang=es-es) may be effective while causing fewer side effects. This has

been observed in children, too, especially in those aged less than 7 years.[8] The CDC recommends doses of 5 to 7 mg/kg/day in children aged less than 12 years.

In brief, controlling the VT of CD requires the improvement of screening programmes, which should not be limited to pregnant women but include all women of childbearing age. The standardisation of screening protocols and training of health care professionals are essential for the correct assessment and management of this disease. Improving the diagnostic algorithms applied to newborns is key to prevent losses to follow up. Lastly, improvements in available treatments by optimising drug dosage, combining drugs to increase effectiveness and reducing the incidence of adverse events are of vital importance for the future control of the disease.

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