Screening and Management of Children at Risk for Chagas Disease in Nonendemic Areas

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Chagas disease bears the highest burden among parasitic diseases in the Western Hemisphere and generates considerable health-related costs. Considered as a neglected tropical disease by the World Health Organization, it is caused by the infection with the protozoa Trypanosoma cruzi. Transmission is mainly vector-borne through the inoculation of infected reduviid bugs’ feces, but it can also be acquired vertically, which remains the predominant route outside endemic areas.

In Europe and other nonendemic countries, the number of imported cases is rapidly increasing due to the migration of large populations at risk. Whereas most reported cases concern adults at the chronic stage, congenital and Pediatric cases are poorly identified and reported due to the frequent lack of systematic screening programs in countries at risk. Infected newborns and children bear risks of long-term and potentially life-threatening complications.

EPIDEMIOLOGY AND TRANSMISSION

Chagas disease is endemic in South and Central America, wherein 70 million individuals are at risk and 5–6 million are estimated to be infected. According to the available data, approximately 9000 newborns acquire the infection congenitally each year.2 In Europe, Spain is particularly affected with 60,000–80,000 cases, whereas 100,000–300,000 persons are infected in the United States.3 The emergence and transmission of the disease in nonendemic countries are fueled by the frequent lack of health professional awareness, insufficient health policies and the mostly silent course of the infection.

Several transmission routes coexist1:

1. Vectorial: Vectorial transmission remains the main cause in endemic areas. The vector is a blood-sucking reduvid insect (Triatoma subfamily), known as the kissing bug. It typically lives in the cracks of mud walls and roofs in rural housing and also increasingly in periurban areas, and individuals are repeatedly exposed to the vector and the parasite. Their feces, containing the parasites, are left on the host’s skin after a blood meal. Crossing skin or mucosal barriers, the trypanosomes reach the muscles and ganglion cells through the lymphatic system and bloodstream.

2. Oral: Food (eg, berries, sugarcane and fruit juices) can be contaminated by reduviid feces. With increasing food chain-vector contacts in endemic areas, it is an emerging transmission route.

3. Vertical: The rate of mother-to-child transmission is around 5% overall, with rates depending on mothers’ parasitemia and is thus frequently lower outside endemic areas.4 Transmission through breast-feeding has never been reported.

4. Blood transfusion and tissue or organ transplantation: Since the recent scaling-up in blood bank screening programs in Latin America, this transmission route is of lesser importance. However, cases continue to be reported, including in nonendemic countries where such measures are still incompletely implemented.

CLINICAL PRESENTATION

The acute phase begins after an incubation period of 7–14 days. Marked by high parasitemia, it lasts for 4–8 weeks before patients enter the chronic stage. Fever, adenopathies and splenomegaly are rarely found, with 90% of acute infections remaining asymptomatic. Rare complications such as myocarditis and meningitis carry a high mortality rate.
The chronic indeterminate phase is defined by a positive serology without any clinical manifestation and a normal electrocardiogram. Although two-thirds of infected individuals remain at that stage without developing symptoms and signs of evolution, they remain infectious, even if they never develop symptoms.

The chronic determinate phase appears decades (10–30 years) after the initial infection and is characterized by cardiac, digestive or mixed progressive disorders. Among these patients, 20%–30% will develop cardiac damage with distinct clinical pictures. Dilated cardiomyopathy, conduction anomalies, malignant arrhythmias and thromboembolic events result from the chronic myocardial inflammation mediated by T. cruzi persistence and probably concurrent immunologic response imbalance. The advanced stages of cardiac damage expose patients to a higher mortality than ischemic heart disease. The lack of specific signs and symptoms also cause a frequent delay in diagnosis and management.

Neural cell destruction in the digestive submucosae leads to progressive loss of motility and dilatation. Ultimately, megacolon and dilatation. Megacolon and during the early reactivation.

At the chronic stage, its limited sensitivity (60%–90%) precludes its systematic use as a diagnostic test. Its persistent positivity after treatment attests for treatment failure.

Elevated parasitemia—demonstrated by quantitative PCR—has been shown to increase the risk of vertical transmission in pregnant women. PCR may allow earlier detection of congenitally infected newborns compared with microscopy, but its use is still limited by technical issues, possibly false-positive results due to nonviable parasites and poor availability outside tertiary centers. In Geneva, between 2008 and 2014, only 1 in 6 congenitally infected neonates had a positive PCR at birth.

**Serology**

In the chronic phase, diagnosis relies on serological methods that include enzyme-linked immunosorbent assay, indirect immunofluorescence and indirect hemagglutination assays. Given possible cross-reactivity with other kinetoplastids, the use of 2 different serological techniques is recommended. Rapid tests have been recently developed and represent an interesting addition to serology. Although their sensitivity and specificity are lower than traditional assays, their ease of use may partly compensate for this disadvantage, especially as a screening tool in the community, in case of emergency and at the time of delivery in the absence of prenatal screening of high-risk mothers. Yet, confirmatory test with standard serology is required to definitively assess infection status.

**TREATMENT RESPONSE EVALUATION**

In adults, evaluation of treatment efficacy is hindered by the absence of a test of cure. Indeed, serology remains positive for many years after treatment and is thus of limited value for short-term follow-up. Antibody titers decrease faster after treatment in children infected for <2 years, which makes it the method of choice to assess treatment response in congenitally infected children. In Bolivian newborns treated in the neonatal period, most (90.7%) patients had negative serologies after 10 months. PCR is limited by its poor pre-treatment sensitivity, and a negative result is of uncertain clinical significance.

**TREATMENT**

Antiparasitic treatment is necessary for all infected children, particularly those <14 years, given its good tolerance and efficacy. In women of child-bearing age, it decreases the risk of vertical transmission when given before pregnancy. It is recommended during the acute phase, in case of reactivation and in presence of severe immunosuppression. Evidence points to a protective effect against the development or evolution of cardiac damage in young-to-middle age adults at the indeterminate phase. In older patients and once cardiac damage is present, treatment does not appear to alter the course of the disease.

Nifurtimox and benznidazole are the 2 available antitrypanosomal therapies. Both are usually well tolerated by children. However, because of a better tolerance profile and a pediatric formulation to be released soon, benznidazole is usually used as first-line treatment. Both are contraindicated during pregnancy. The most frequent adverse reactions with benznidazole are dermatological manifestations (rash) and neurological complaints (headache, blurry vision, dizziness and paresthesia). Rare cases of Stevens-Johnson syndrome have been reported. Biochemical anomalies include leukopenia and increased liver function tests. Serious adverse events mandating treatment interruption are infrequent in children. Nifurtimox may cause digestive symptoms. Both drugs are contraindicated during pregnancy.

Cure rate, as assessed by seronegativity, is correlated with the timing of treatment. Successful cure is highest during the first year after infection (>90%). For this reason, early screening and treatment in infants is indicated. An algorithm is proposed in Figure 1.

**SCREENING FOR CONGENITAL CHAGAS DISEASE**

The latest recommendations for nonendemic countries are summarized below:

- Chagas serology should be performed in all pregnant women: (1) who live in endemic areas (from Mexico to Argentina, except the Caribbean); (2) who were born or who lived in an endemic area or whose mother was born in an endemic area or (3) who received an uncontrolled blood transfusion in an endemic area. When positive, screening and follow-up of the newborn are mandatory. Treatment for the mother should be proposed after delivery and breast-feeding.
- Newborns of infected mothers need thorough clinical assessment and direct blood microscopic examination (cord or peripheral venous blood). PCR might be useful for earlier diagnosis but entails a risk of false positive. Currently, lack of standardization and limited availability preclude its universal use.

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**CHAGAS AND IMMUNOSUPPRESSION**

Immunosuppression may lead to T. cruzi reactivation. In the presence of HIV infection with low (<200 cells/mm³) CD4 count, myocarditis or toxoplasmosis-like encephalitis predominates, whereas in drug-induced immunosuppression such as post-transplant regimen, cutaneous or cardiac symptoms are most frequent. These life-threatening conditions require urgent identification and response depending on prompt treatment initiation. As a preventive measure, all patients from endemic areas (or having a mother from Latin America) should be screened for Chagas disease before starting immunosuppressive therapy.

**DIAGNOSIS**

Diagnostic strategies differ according to the stages of the disease.

**Direct Microscopic Examination**

In the acute phase, the trypanosomes can be visualized in blood (thick/thin smear or concentration techniques). This technique is also useful to detect reactivations in immunosuppressed patients and infection in newborns. Due to low parasitemia, it is frequently negative during the chronic phase.

Blood polymerase chain reaction (PCR) is highly sensitive in the acute phase and during the early reactivation.

When positive, screening and follow-up of the newborn are mandatory. Treatment for the mother should be proposed after delivery and breast-feeding.

- Newborns of infected mothers need thorough clinical assessment and direct blood microscopic examination (cord or peripheral venous blood). PCR might be useful for earlier diagnosis but entails a risk of false positive. Currently, lack of standardization and limited availability preclude its universal use.
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Chagas in Children in Nonendemic Areas

Due to the poor sensitivity of direct examination, screening of infants born from infected mothers have to be completed by a serological test at the age of 9 months onward after clearance of maternal antibodies. This reduces the risk of loss-to-follow-up, and all measures should be taken to properly inform mothers of this necessary examination. In the case of a positive result, treatment must be started as early as possible.

All children coming from Latin America (including adopted children) should be screened (except if they were born in nonendemic areas and if the mother has a negative test). In the case of a positive result, treatment must be started. Overall, detection of a positive case should include a whole-family approach with testing of siblings and relatives. Close clinical and biological follow-up is necessary during treatment, and mothers should be informed about early signs of treatment intolerance.

A whole-of-family screening is mandated once a case has been identified. To assess treatment success in children, we propose to perform an annual serology until it becomes negative. However, there is no universal recommendation for biological follow-up.

CONCLUSIONS

Chagas disease is an insidious and potentially life-threatening disease rapidly emerging outside Latin America. Infected children are at high risk of remaining undetected, given the low awareness among health professionals, the absence of clinical manifestations and the lack of systematic screening programs. Early treatment of infants and young children ensures a high cure rate, and all pregnant women from endemic areas should be screened. In the case of maternal illness, children should be tested and treated as early as possible when positive.

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