American trypanosomiasis (Chagas' disease)

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Summary

- *Trypanosoma cruzi*, only in the New World
- Transmission via bugs, blood transfusion, congenitally and orally (bug feces in food/drink)
- Importance of poverty (housing) in transmission
- Acute (especially children): chancre, Romaña's sign, fever, lymphadenophathy, myocarditis, hepatosplenomegaly
- Chronic: cardiac arrhythmias, heart failure, emboli, apical aneurysms
- Chronic: dysphagia, constipation (mega-syndrome)
- Diagnosis: clinical + thick smear/buffy coat (early), serology, xenodiagnosis, ECG, X-ray (late), PCR
- Treatment in the early phase still reasonably successful with medication; in the late phase difficult and probably useless
- Nifurtimox badly tolerated as a 2 to 4-month treatment; benznidazole: problems with bone marrow toxicity, hypersensitivity, peripheral neuropathy.
- Prevention: much progress in recent years via vector control and control of blood banks.

Introduction

Historical note

In 1907 the physician Carlos Chagas (1879-1934) was working in Lassance, a small poverty-stricken town on the Sao Francisco river in the state of Minas Gerais, Brazil. The town had been built along the railway from Rio de Janeiro to Belem. Chagas treated the workmen for injuries, syphilis, malaria etc. He noticed that cardiac arrhythmias occurred frequently. One day an engineer brought him an insect of the type which was known to often suck the blood of humans at night. Chagas wondered if this creature could also transmit malaria like the Anopheles mosquitoes. In the bug he discovered a unicellular parasite. In April 1908 he found the same parasite in a sick cat. Two weeks later, in the same house, the parasite was found in the blood of a 3-year-old child (Rita), who was ill with fever. Her face, liver, spleen and lymph nodes were swollen and the child died shortly afterwards. In the house there were countless bugs which tested positive for the parasite. He sent bugs to Rio, to Oswaldo Cruz, his former teacher (Brazilian physician 1872-1917).

In the laboratory the parasite caused an infection in marmoset monkeys (Callithrix sp.), rodents and puppies. The disease caused by this parasite, American trypanosomiasis, was named after Chagas. The parasite was given the name Trypanosoma cruzi. The parasite did not always trigger disease, however. In 1908 Chagas also discovered the parasite in another person (Bernice). This woman died in 1989, still infected, but without signs of organ involvement.

The infection apparently already existed before contact with the West. In 1985, 22 mummies were found in the Andes mountains. These were 1500 years old. In approximately half of them the heart, colon and/or oesophagus were clearly enlarged (lesions typical for Chagas' disease). *Trypanosoma cruzi* DNA was found in 1999 in a 4000 year-old mummy in Northern Chile. In one of his books Charles Darwin describes how in 1835 in South America he was bitten by the bugs. It is possible that he incurred infection and later developed a chronic form of the disease.

Distribution

The infection only occurs in America in endemic regions. It is a disease associated directly with poverty. The severity varies from region to region. In the South of Texas there are very few cases. Infections occur in Central America sporadically. Although the disease is endemic in large areas of South America (in particular in the "Gran Chaco" region), the majority of those infected have no symptoms. Until recently it was thought that approximately 16 million persons were infected, but these figures are under review (see Prevention). The disease is transmitted via the faeces of an infected bug.

Reservoir

The parasite, *Trypanosoma cruzi*, occurs in more than 100 species of mammal (opossums, guinea pigs, goats, dogs, cats, rats, mice, and so on). There are several known (and probably also some unknown) subtypes each of which has its own distribution and probably also its own pathogenic features. In view of the extent of the animal reservoir eradication of the parasite will not be possible. This does not mean that the disease and the transmission cannot themselves be controlled. At present the strains are divided into two groups. *Trypanosoma cruzi* I has an extensive sylvatic reservoir, of which opossums appear the most important. This group is not very common in the "Southern Cone" countries (Argentina, Brazil, Chile, Paraguay, Uruguay), but it is virtually the only form which occurs north of the Amazon region. T. cruzi II seems to be chiefly associated with rodents and is common in the Southern Cone.

Transmission

Transmission occurs chiefly **via infected bugs.** These large insects like to bite sleeping humans at night (a mosquito net gives protection). They have a sharp proboscis which at rest is folded below the head like a jack-knife. When biting they inject anticoagulants and an anesthetic substance into the wound. Since this makes their bite quite painless (kissing bugs), people seldom wake up and several bites may take place unnoticed in the course of one night. The parasite is not inoculated directly by the bite, as Chagas initially thought. In 1913 Brumpt showed that the parasite is found in the faeces of the insect. While the animals suck blood, they defecate. By scratching, a bitten person can bring the faeces into the bite wound or rub them into the conjunctiva. The parasites multiply in humans and then appear in the blood. The cycle is completed when a subsequent bug drinks infected blood. In the bug the parasite undergoes further changes and after 2 to 3 weeks is excreted with the faeces during a subsequent bite. It is estimated that the risk per bite by an infected *Triatoma* is one in a thousand. The existence of **oral transmission** has been suspected for quite a while. It was demonstrated in animals and has now been confirmed in some human cases. How frequent oral transmission happens is not clear yet. Food or drink contaminated with the liquid faeces of infected bugs or containing (crushed) dead bugs may lead to infection not only in experimental animals but also in humans. Small outbreaks of acute Chagas are regularly reported from Northern Brazil in the last years. The parasite could withstand short periods of freezing, but not decontamination with sodium hypochlorite or heating to 80°C. **Congenital infection** (1 to 2 % risk) and transmission via **blood transfusion** also occur (poor people often sell their blood). To give an idea of the scale, this implies for example that several thousands of babies are born with congenital Chagas each year in the USA, and a lesser number in Europe (from immigrant mothers from endemic areas). Transmission via transfusion is particularly important in urban zones and has been reported outside endemic countries. The risk of infection after a contaminated blood transfusion is estimated at one in five. There are sporadic cases of **accidental contamination** of laboratory staff (finger prick, aerosol) and after **organ transplantation** (including in non-endemic countries).

Vectors

The bugs are also known locally as "vinchucas" or "barbeiros". Of the approximately 120 vector species only about 7 are important. Each species has its own region of distribution:

- Central America and northern South America: *Triatoma dimidiata* and *Rhodnius prolixus*
- South America (south of 5° S): *T. infestans*, *T. braziliensis*, *T. sordida*, *Panstrongylus megistus*

The bugs mentioned here are the main vectors. Other bugs also play a part in different regions. The

bugs each have their own preferred biotopes. *T. dimidiata*, for example, is often found inside houses on the floor or the lower 150 cm of the walls or immediately outside in dung heaps, hollow trees, etc. In contrast, *R. prolixus* prefers to live in palm leaves either in the roof of the house or in the tree itself. In and around the house the bugs can feed on animals (e.g. dogs are important because they sleep at night when the bugs are active). The vectors often live in chicken runs but the chickens themselves are not infected (they do eat bugs). During the day the insects hide in all kinds of cracks and crannies (importance of earthen or adobe walls) and in the roofing (straw, wood, etc). It can be seen immediately that the key word in Chagas' disease is "poverty". These are insects which reproduce slowly and whose geographical spread is slow. Migration of bugs, by migrating birds for example still needs to be studied. In view of these characteristics and the fact that the important vectors live around houses they can easily be reached by eradication campaigns.

A fertilized female lays several hundred eggs in her lifetime. From the egg comes a nymph which always needs a blood meal for its subsequent development stages (both sexes suck blood). The last instar will develop into an adult insect. During a blood meal they suck more than their own weight in blood. This takes 10-25 minutes. The insects may live for up to 2 years (5 years for *T. barberi*). *Rhodnius prolixus* has a relatively short generation time (3-5 months), while for *T. dimidiata* this time is quite long (1 year or longer). Long generation times make the development of resistance to insecticides difficult.

Parasite

In stained blood preparations the parasites are C- or S-shaped with a prominent kinetoplast towards the rear (trypomastigotes). The nucleus is elongated and the undulating membrane is usually not clearly visible. After infection multiplication of the parasite in the human is solely intracellular. They form microscopic pseudocysts in the tissues (similar to toxoplasmosis and sarcocsytosis). This occurs mainly in the heart, muscle cells, some nerve cells and the lymphatic system. In the cell the parasite is small and rounded with no flagellum (amastigote). When the infected cell ruptures, parasites are released into the blood circulation where they become elongated and develop a flagellum. These forms can then infect other cells or be ingested by a bug.

Clinical aspects

Infection and incubation

Incubation period after exposure to vector-borne *T. cruzi* is 1 to 2 weeks, although longer incubation times are sometimes reported. If the parasites penetrate via the conjunctiva, there is unilateral

redness and oedema of the upper and lower eyelids after 4 to 12 days. This is "Romaña's sign", named after the Argentinean physician Cecilio Romaña, who described the oedema in 1935. This swelling may last for weeks. Sometimes there is also swelling of the ipsilateral lymph nodes (including the pre-auricular lymph nodes). Trypanosomes may be found in the tears at this stage. If inoculation is in the skin there is local oedema and redness ("chagoma") in 75% of cases. This remains for 1 to 4 months. From these sites the infections spreads.

Acute stage

The incubation period is followed by the acute phase which lasts 4 to 8 weeks. Many infections are initially asymptomatic. Acute symptoms occur more frequently in children than in adults. Dissemination of the parasite from the inoculation site may go unnoticed but may also give rise to acute illness with muscle pain, local or generalized oedema, swollen liver, spleen and lymph nodes. Moderate fever is almost always present in symptomatic cases and may persist for a long time, two or even four months. Sometimes there is also acute inflammation of the heart (myocarditis) with arrhythmias, decreased blood pressure, and heart failure. As with other forms of myocarditis the electrocardiogram is frequently abnormal. There is low QRS-voltage, prolonged PR- and/or QT-interval, T-wave abnormalities. Rarely there are ventricular extrasystoles or atrial fibrillation (the prognosis is poor if this occurs). Acute inflammation of the brain and meninges (meningo-encephalitis) occurs, chiefly in young children. Inflammation of the heart and brain may be fatal. There is pronounced lymphocytosis and monocytosis. The acute-phase case fatality rate is nowadays estimated to be 0.25 to 0.50% with early treatment.

Latent period

If the patient survives the initial phase (which is usually the case), a latent period occurs of indeterminate duration. The patient is asymptomatic, seropositive and the parasitemia is very low. Focal lesions are found in 60% of endomyocardial biopsies from patients in the latent phase. A positive xenodiagnosis can be obtained in 50% to 100% of these patients. For xenodiagnosis 10 to 40 non-infected bugs (e.g. *Dipetalogaster maxima* or *Triatoma infestans*) feed on blood from the patient. The faeces from these animals are investigated after 30, 60 and 90 days. In the event of immunosuppression there may be an acute flare-up, including meningo-encephalitis associated with AIDS or heart transplantation.

Chronic phase

Gradually the patient develops symptoms. These vary greatly from region to region. Lesions of the heart, oesophagus and colon are the most common.

Chronic heart problems

Chronic damage to the heart muscle cells and the cardiac conduction system (including that caused by auto-immune mechanisms) leads to heart failure. There is dyspnoea during exertion, orthopnoea and sometimes paroxysmal nightly dyspnoea, oedema of the feet and ankles, congestion of the neck veins, enlarged liver and crackles over the base of the lungs. Sometimes there is pulsus alternans: the peripheral arterial pulsations are alternately strong and weak. The precise pathophysiological mechanism is not fully known. The apex of the heart, which is normally situated on the mid-clavicular line, is displaced to the left. The heart sometimes becomes enormous, which may lead to clot formation in the heart. If blood clots break loose, there may be embolic complications: cerebrovascular accident (CVA), ischemia of limbs, renal infarction. Apical lesions in the left ventricle (wall thinning, intramural bleeding, aneurysms) are typical and occur in approximately 50% of patients. Unlike arteriosclerotic post-infarction aneurysms, in Chagas' disease the apical cardiac tissue does not consist of scar tissue, the wall is simply thinned. Right ventricular lesions occur in 10 to 20%. Cardiac arrhythmias may cause palpitations, dizziness, syncope and sudden death. On the electrocardiogram a right bundle branch block is often seen, together with a left anterior hemiblock, ventricular extrasystoles, abnormal Q-waves and/or AV-conduction disturbances. The coronary arteries are normal. A complete left bundle branch block is exceptional, unlike in idiopathic dilated cardiomyopathy. Sudden death is common in people with Chagas' disease. Probably this is due to ventricular tachycardia which changes suddenly into ventricular fibrillation.

In advanced heart failure, typical radiographic signs may be observed on a chest X-ray: cardiomegaly, prominent hili and distended pulmonary veins in the upper fields, pleural fluid, interstitial pulmonary oedema (fluid in the interlobular septa with Kerley B lines), peribronchial cuffing and finally alveolar pulmonary oedema ("butterfly oedema").

The degree of heart failure is often indicated using the New York Heart Association classification:

- Grade I : asymptomatic
- Grade II : symptoms only during moderate to severe exertion
- Grade III : symptoms during mild exertion
- Grade IV : symptoms at rest. Patient generally confined to bed/chair.

Oesophagus and colon problems

Due to involvement of the small nerves in the oesophagus and colon, peristalsis is reduced and these organs are distended. This occurs in 5 to 10% of seropositive people south of the Amazon, and is virtually absent further north. *Trypanosoma cruzi I* and *II* are both associated with cardiac lesions, but intestinal lesions only occur in infection with *T. cruzi II* (the southern area).

Mega-oesophagus is characterized by difficulty in swallowing (dysphagia), choking, hiccups and nocturnal cough. This often leads to under-nourishment and loss of weight. Aspiration pneumonia is the most feared complication with substantial mortality. A clinical aid for detecting delayed oesophageal emptying is to measure the time between swallowing a mouthful of water, and observing the abdominal noises (stethoscope on the epigastrium). Normally this is less than 10 seconds. A distended oesophagus may also be shown on X-ray. The parotid gland may hypertrophy and lead to so-called "cat's face".

Mega-colon can lead to pronounced constipation, meteorism (abdominal distension), abdominal pain and functional intestinal obstruction due to involvement of the myenteric (Auerbach) plexus and the submucosal (Meissner's) plexus). The abdomen is often distended. Fecaloma, volvulus and peritonitis are complications.

The nervous system

In no other infectious disease is the involvement of the autonomous nervous system as important as in Chagas' disease. Denervation of the parasympathetic nervous system is better documented and is much more pronounced than denervation of the sympathetic system. There can be sensorimotor polyneuritis. There is some hypoesthesia and paraesthesia, but chiefly a reduction or loss of tendon reflexes. The EMG is disturbed. In the central nervous system there is meningo-encephalitis in the acute phase, but the abnormalities in the chronic phase need to be better defined. In flare-up (e.g. AIDS) there may be intracranial hypertension, lesions of the cerebral nerves, paresis, plegia, stupor and convulsions. The cerebrospinal fluid exhibits a normal number of cells or pleocytosis with predominant lymphocytes and an elevated protein content. At times *T. cruzi* may even be detected in the cerebrospinal fluid. A CT scan of the brain shows one or more necrotizing lesions which may or may not be ring-shaped, with haemorrhages usually subcortical in the brain hemispheres and occasionally in the cerebellum or the brain stem. *T. cruzi* lesions rarely occur in the basal nuclei. These clinical pictures should be differentiated from cerebral toxoplasmosis, abscesses, mycoses, tuberculomata or other mycobacterial lesions, metastases or lymphoma.

Of all cerebral vascular accidents leading to stroke, about 20% are secondary to embolism from a blood clot secondary to atrial fibrillation. If patients do not take oral anticoagulants, an average of 5% CVA's per year can be expected, which roughly translates to 50% of patients with CVA within 10 years after onset of atrial fibrillation. However for several reasons (mostly haemorrhagic) 20-40% of patients cannot be treated with oral anticoagulants. Most of the clots (90%) originate when blood stagnates in the left atrial appendage, also known as the left atrial auriculum.

Congenital infection

About 1 to 2 % of babies born to seropositive mothers are infected. They may be asymptomatic (rarely) or may develop hepatosplenomegaly, neurological involvement, myocarditis, oedema and a bleeding tendency. The babies may be dysmature and/or premature. Fever is rare in these children. The mortality may be as high as 50% and they tend to die within a week. Those who survive will generally have permanent residual neurological damage.

Diagnosis

In the acute stage the parasite may be found in the blood via a thin **blood smear**, thick smear or buffy coat. As a concentration technique an anion-exchange minicolumn may be used (Woo's technique similar to Lanham's column, but with a different buffer, see African sleeping sickness). Strout's concentration technique includes the double centrifugation of serum (from 10-20 ml of blood), after which the motile trypanosomes can be detected in the sediment. **PCR techniques** for *T. cruzi* exist, but can only be carried out in better equipped laboratories. The **serology** is positive from the fourth week. To know whether the neonate from a seropositive mother is infected, PCR is performed and IgM antibodies in its blood are determined. A positive serology (IgG) 6 months after birth also indicates infection. In-vitro and in-vivo culture is possible, but usually not available. Biopsies of lymph nodes, heart and muscles sometimes show parasitic pseudocysts (amastigotes in the cells). This is quite an aggressive technique and not very sensitive.
Dipetalogaster maximus is a blood sucking bug which can take up to 4 ml of blood in one meal. It is best known for its use in xenodiagnosis (cfr. supra, latent period) of Chagas' disease.

Following WHO recommendations in patient with latent infection (indeterminate), 2 or 3 different positive serological tests are required before ascertaining the diagnosis of Chagas disease.

Prognosis

In an endemic region an asymptomatic person with positive serology is probably a carrier

(xenodiagnosis positive in 50 to 100 % of cases). The percentage of seropositive persons who develop symptoms is highly dependent on the geographical region (e.g. 10 to 30%). Some people have mega-organs but are asymptomatic.

Chagas' disease variables associated with adverse outcome

- 2 points: Male
- 2 points: Low QRS voltage on ECG
- 3 points: Non-sustained ventricular tachycardia on 24-h Holter monitoring (run of 3 or more consecutive VES, with a frequency >100).
- 3 points: Left ventricular systolic dysfunction: segmental or global wall-motion abnormality on echocardiography (quid apical aneurysms, intracavitary thrombus)
- 5 points: NYHA III or IV
- 5 points: Cardiomegaly present on CXR, defined as a cardiothoracic index > 0,5

Results:

- < 6: low risk 14% mortality rate in 10 years
- 7- 11: intermediate risk 44% mortality rate in 10 years
- 12-20: high risk 84% mortality rate in 10 years

Treatment

Acute phase

The acute phase lasts up to 60 days. All patients who are in this phase should be treated.

Congenital infection

All infected children should be treated. The earlier therapy is begun, the better the results.

Chronic phase

Etiological drug treatment is indicated for "recent" chronic infections (a few years). In practice all children younger than 10 years are treated. If mega-oesophagus is already present the dysphagia should be treated (the passage and absorption of oral medication may be severely impeded).

Etiological treatment in these latter patients was not advised formerly but more recent data have brought this into question. In a study in Argentina, 131 patients with chronic Chagas' disease were treated with benznidazole. After an average follow up of 8 years, 4.2% exhibited ECG changes compared to 30% in the untreated group. There was also considerably less clinical deterioration in the treated group (2.1% compared to 17%).

The results of a large multicenter prospective study (the BENEFIT study) has however recently demonstrated that an etiologic treatment with benznidazole did not provide any clinical benefit when a patient with chronic infection had already developed a cardiomyopathy (no reversibility). Treating this group of chronic patients appear to be futile while exposing them to some drug toxicity. Whether this is also true for a patient with latent infection and no complication (yet) will require additional evaluation. Such studies are however very difficult to conduct due to the very long latency period to obtain robust clinical outcome data.

Accidental infection

This may occur for example in laboratory staff. A serum specimen should be frozen before beginning treatment and a second blood sample taken 4 weeks later. Serology is performed on these paired sera. Benznidazole 7-10 mg/kg/day x 10 days is the usual treatment regimen in this situation.

Transplant patients

There are two possible situations: transplantation of an infected organ into a non-infected patient and transplantation of a healthy organ into an infected patient. A donor may be infected so that the recipient becomes infected. Normally the donor is tested beforehand and positive donors are refused, but nevertheless these situations sometimes occur. Alternatively transplantation may be carried out on a patient who is a chronic carrier. The immune suppression that these patients undergo [steroids, azathioprine (Imuran®), tacrolimus (Prograft®) and cyclosporine (Sandimmun®)], may lead to reactivation of Chagas' disease. In both cases treatment with benznidazole 5 mg/kg/day x 60 days, is indicated.

HIV patients and Chagas

Infection with HIV may lead to significant flare-up of Chagas' disease. In endemic regions all HIV patients should be monitored for Chagas' disease. If positive, benznidazole is recommended. There is insufficient data concerning chemoprophylaxis. Since the initial step is often serology, one would

normally first try to confirm the diagnosis with a second serological test (ELISA-based preferably) and by looking for circulating parasites by microscope (QBC or buffy coat), PCR and perhaps xenodiagnosis. If the diagnosis is confirmed, the patients deserve to be treated as their risk of severe complications (cardiac, digestive or CNS) is high. Benznidazole is preferred to nifurtimox, since nifurtimox is a treatment that is really badly tolerated in adults (notably a lot of nasty allergic reactions). Benznidazole 5mg/kg (max 300mg) daily for 60 days is not an easy treatment to administer neither (beware of skin toxicity!).

Pregnancy

Treatment during pregnancy is not recommended, although congenital Chagas has been well documented. It is clear that more understanding and better outcomes are sorely needed. Infants of infected mothers have to be carefully followed-up to early detect congenital Chagas.

Treatment: Drugs

There are several problems. The drugs have an unsatisfactory cure rate. The chronic lesions may be caused by auto-immune mechanisms and might not be improved by eradicating parasites (as suggested by the recent BENEFIT trial). Parasites play however some role since the disease worsens during immune suppression as in transplantation and in HIV. The drugs should be given long term (minimum 2 months). Results vary from country to country, possibly due to a difference in parasite susceptibility. Side effects occur more often in adults than in children. It is best to avoid steroids or other immunosuppressive drugs, since these may exacerbate the infection.

Nifurtimox (Lampit®) 5 mg/kg/day orally, slowly increased to 15 mg/kg/day (divided over 3 doses) for 2 to 4 months. There are regular problems for the sustainability of its production. Side effects: neurotoxicity (insomnia, tremor, polyneuritis), nausea, leukopaenia, thrombocytopaenia or hypersensitivity. May cause haemolysis in G6PD deficiency [glucose-6-phosphate dehydrogenase]. In the acute phase the parasites disappear from the blood in 80 % to almost 100 % of cases. The actual cure rate is 50-60%. In a prospective study conducted in Switzerland among Bolivian immigrants, more than 90% of the patients developed some side-effects, sometimes severe (angioneurotic oedema, Dressler syndrome) and half had to discontinue the drug before the end of the 2-month therapy.

Benznidazole (Radanil®, Ragonil®, Rochagan®) 5-10 mg/kg/day orally for 1 to 2 months. Administration (generally 100 mg tablets) is twice daily. The same side effects as nifurtimox, but less

frequent and less pronounced, although skin rash occurs relatively frequently (up to 30-40% of patients, with probably some genetic predisposition) sometimes accompanied by swollen lymph nodes or angioedema. The pharmaceutical company Roche has donated all commercial rights and the technology to manufacture benznidazole to the Brazilian government. In all countries 2-month treatment is recommended, except in Argentina where experts recommend a one-month treatment only.

Other types of drugs for treatment

Posaconazole, an anti-fungal therapy, was found to be inferior (in terms of parasitological failure) to benznidazole in a randomized control trial in Spain, published in 2014.

Fexinidazole has a clear anti-*T. cruzi* in vitro activity, but no clinical study has taken place so far.

Ravuconazole is a new triazole with in vitro activity against species of Candida, Cryptococcus and Aspergillus, but also in vitro and in vivo (mice) activity against *Trypanosoma cruzi*. Ravuconazole has a long half-life in humans, which hopefully will facilitate compliance in patients. Clinical trials for its use in Chagas' disease are ongoing in Bolivia.

In the chronic phase the usefulness of these drugs could not be demonstrated (BENEFIT Trial) at least in patients having already (mostly heart) complications.

Symptomatic therapy is therefore indicated: oesophageal sphincter dilation, extramucosal cardiotomy (Heller's operation), colon surgery. An experimental treatment is the endoscopic injection of botulin toxin into the distal oesophageal sphincter (e.g. 20 U into each quadrant).

In heart failure diuretics, ACE-inhibitors and antiarrhythmic drugs may be beneficial. Beta-blockers are best avoided in view of the AV-conduction problems and brady-arrhythmias. Aspirin or anticoagulants are indicated for patients with atrial fibrillation, previous embolic phenomena and apical aneurysms. Amiodarone (Cordarone®) is effective in more than 50% of patients who develop ventricular extrasystoles or ventricular tachycardia. A bifascicular or trifascicular conduction block, also a second or third degree AV-block are contra-indications. A high incidence of "torsades de pointes" has been observed during use of disopyramide and other class I antiarrhythmic drugs.. Pacemakers, automatic defibrillators and cardiac surgery (including heart transplantation) are reserved in practice for those with financial means and these persons have an inherently low risk of infection. It is obvious that such

costly procedures will not be within the financial means of the average Chagas' patient.

Prevention

The animal reservoir of *Trypanosoma cruzi* cannot be eradicated. There is no vaccine. Chagas' disease is typically a disease of poverty. Improvements in housing (brick or plaster walls, corrugated iron roofs, long-acting insecticides on house walls) diminish the insect population. A mosquito net has also proven usefulness here. Serological testing of the blood used for transfusion is very helpful. To date the various biological methods of eradication of the vectors (insecticide sprays, increasing natural enemies) which have been tested have not been effective because a new ecological balance is very quickly achieved but have brought substantial control in most regions.

In 1991-92 the "Southern Cone Initiative" project was launched by Argentina, Bolivia, Brazil, Chile, Paraguay and Uruguay with the objective of stopping the transmission of Chagas' disease. In 1997 Peru joined the project. After an initial phase for preparation (charting the foci, programming the activities, calculating the costs) there was an attack phase with insecticides, repeated after 3 to 6 months. Insecticide-containing paint is cheaper than the traditional insecticides which are applied by spraying. Insecticides dispersed by fumigant canisters were also used. These are locally produced e.g. in Argentina, are cheap, effective and also active against *Aedes aegypti*, the important dengue vector. At present there are effective colourless long acting insecticides. The fact that people see the bugs, cockroaches, etc. lying dead after spraying is a bonus which makes it easier to accept the spraying procedure. In the Southern Cone Initiative, 1,800,000 houses were treated with pyrethroids (deltametrine, lambda-cyhalotrine, cyflutrine) by the year 2000.

Since then there has been further selective treatment of the houses which still exhibited infestation with triatomes. Simple "sensor boxes" of cardboard (traps for the bugs) were placed in the rooms and the occupants themselves could simply ascertain the presence of triatomes. The last phase is surveillance for the detection of residual foci. This is decentralized and involves the population. The effectiveness of the control program has been demonstrated by the very pronounced drop in seropositivity among young children. The surveillance phase has been reached in 6 countries of the Southern Cone. At present there are several South American countries (Colombia, Ecuador, Venezuela) which have a national control program. Similar programmes were begun in Central America in 1997: Costa Rica, El Salvador, Guatemala, Honduras, Nicaragua, Mexico and Panama. These programs can only be successful if there is participation of the population and if they can be continued for long enough. The latter is a political decision.

In July 2007 the WHO Global Network for Chagas Disease Elimination was launched in order to

coordinate global efforts to eliminate this disease. It includes also many non-endemic countries (such as Spain or USA) where Chagas disease in Latin American immigrants have given rise to a substantial number of secondary transmission (by blood transfusion or transplantation), requiring locally adapted control efforts (screening).

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