A family cluster of Chagas disease detected through selective screening of blood donors: Case report and brief review

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Chagas disease (CD) is a zoonotic disease caused by Trypanosoma cruzi, which is transmitted by triatomine insect vectors in parts of Latin America. In a nonendemic country, such as Canada, spread can still occur via vertical transmission, and infected blood or organ donations. The Canadian Blood Services and Héma-Québec have both implemented selective screening of blood donors for CD based on risk factors. In 2011, Héma-Québec identified two seropositive ‘at-risk’ Chilean siblings who had donated blood in Montreal, Quebec. They were referred to the JD MacLean Centre for Tropical Diseases (Montreal, Quebec) for confirmatory testing (T cruzi excreted-secreted antigen ELISA, polymerase chain reaction and/or radioimmunoprecipitation assay) and follow-up. Screening of the rest of the family revealed two other seropositive family members (the mother and sister). While their geographical history in Chile suggests vectorial transmission, this family cluster of CD raises the possibility of vertical transmission. Congenital infection should always be considered among CD-positive mothers and pregnant women. With blood donor screening, Canadian physicians will increasingly see patients with CD and should know how to manage them appropriately. In addition to the case presentation, the authors review the transmission, screening and clinical management of CD in a nonendemic context.

Key Words: Blood donor screening; Chagas disease; ELISA; PCR; RIPA; Vertical transmission

In nonendemic countries such as Canada, CD is mainly diagnosed among Latin American migrants (6). Based on the large Latin American immigrant population in the United States, it is estimated that >300,000 Americans have CD (7). In Canada, the demographics are very different, with an estimated 3553 infected immigrants residing in the country in 2010 (6). Limited spread of CD can still occur via vertical transmission, and infected blood or organ donations. The Canadian Blood Services and Héma-Québec have both implemented selective screening of blood donors for CD based on risk factors. In 2011, Héma-Québec identified two seropositive ‘at-risk’ Chilean siblings who had donated blood in Montreal, Quebec. They were referred to the JD MacLean Centre for Tropical Diseases (Montreal, Quebec) for confirmatory testing (T cruzi excreted-secreted antigen ELISA, polymerase chain reaction and/or radioimmunoprecipitation assay) and follow-up. Screening of the rest of the family revealed two other seropositive family members (the mother and sister). While their geographical history in Chile suggests vectorial transmission, this family cluster of CD raises the possibility of vertical transmission. Congenital infection should always be considered among CD-positive mothers and pregnant women. With blood donor screening, Canadian physicians will increasingly see patients with CD and should know how to manage them appropriately. In addition to the case presentation, the authors review the transmission, screening and clinical management of CD in a nonendemic context.

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157

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occur in nonendemic countries through congenital transmission and via infected blood and organ donations. Although only a small number of cases of blood-transmitted CD have been reported in North America over the past 26 years (two in Canada [8,9]), these documented cases are likely to represent the tip of the iceberg because most such infections would be asymptomatic and go undiagnosed.

In May 2010, the Canadian Blood Services (CBS), which provides transfusion services for all provinces except Quebec, implemented selective screening of blood donors for CD using the Abbott PRISM Chagas Assay (a chemiluminescent immunoassay; Abbott Laboratories, USA) (10). Details of this screening program have been described recently (11). As of early 2013, CBS had screened >27,000 'at-risk' donors (based on travel, residence and maternal ancestry) and >80,000 'no risk' donors, and identified 14 seropositive subjects in the first group (0.05%) and one seropositive subject in the second group (0.001%) (12). A similar program had been implemented in March 2009 by Héma-Québec, the provider of transfusion services in that province (13) (www.hema-quebec.qc.ca). As of October 2013, 11,730 at-risk donors have been tested by Héma-Québec, and four confirmed positive donors have been found (Dr Gilles Delage, Héma-Québec, personal communication). In July 2011, this program identified two seropositive 'at-risk' Chilean siblings who had donated blood in Montreal, Quebec. These siblings are part of the family of Chilean immigrants that is the focus of the present article.

CASE PRESENTATION

In 2011, the two siblings, II:3 and II:6 (48 and 46 years of age, respectively [Figure I]), donated blood at a Héma-Quebec clinic. On their donor questionnaires, they both answered affirmatively to all questions in the first group of CD 'at-risk' questions: they were born in Chile to a Chilean mother and had lived in Chile for many years (17 and 15 years, respectively, before emigrating to Canada). Initial screening by Héma-Québec (PRISM Chagas Assay, Abbott) suggested that they were both seropositive, and their status was confirmed by repeat testing using the same assay. They were referred to the JD MacLean Centre for Tropical Diseases at the McGill University Health Centre (Montreal, Quebec) for assessment. Blood was drawn for confirmatory serological testing using a T. cruzi excreted-secreted antigen ELISA (TESA-ELISA) (14,15) and PCR by the National Reference Centre for Parasitology (NRCP) in Montreal. Some samples were also tested using RIPA by Quest Diagnostics (USA). Neither had any cardiac nor GI symptoms, and physical examinations were normal. The brother's (II:3) electrocardiogram (ECG) showed sinus bradycardia, but was otherwise normal. His sister (II:6) had an abnormal ECG with sinus bradycardia and nonspecific T wave changes. Their echocardiograms were both normal. They were asked to bring their parents (I:1, I:2) and their two other sisters (II:2, II:7) to the clinic to be tested for CD.

Their mother (I:2, 67 years of age) and sisters (II:2 and II:7, 50 and 38 years of age, respectively) were tested using TESA-ELISA and PCR at the NRCP. The father (I:1, 70 years of age) declined to be tested. The eldest daughter (II:2) had no cardiac symptoms, although she had noted mild, intermittent diarrhea and abdominal cramps for the past three years. Neither the mother (I:2) nor the youngest sister (II:7) had any cardiac or GI complaints and their physical examinations were entirely normal. The mother's ECG was abnormal, with a right bundle branch block, a prolonged QRS and incomplete left posterior fascicular block. The eldest sister (II:2) had rightward axis deviation with an otherwise normal ECG. The youngest sister’s (II:7) ECG was normal. Cardiac ultrasounds for these three members of the family (I:1, II:2 and II:7) were all essentially normal.

A summary of test results for the first and second generations is presented in Table 1. Four of the five family members tested were found to be positive by ≥1 of the serological assays. Only the youngest sister (II:7) was found to be seronegative for CD. PCR testing was negative for all four of the seropositive family members.

Because CD can be transmitted congenitally, the two CD-positive sisters (II:2, II:6) were advised to bring their five children to the Tropical Diseases Centre for testing (III:1-3 and III:7-8). All were found to be seronegative.

DISCUSSION

A family with four CD-positive individuals is a rare finding in a nonendemic country such as Canada. However, with the introduction of a screening program for blood donors, Canadian physicians will likely encounter an increasing number of newly diagnosed CD patients and will have to educate and manage these patients appropriately. The present case provides a good opportunity to review and discuss issues related to CD diagnosis and treatment.

Transmission

This family cluster raises important questions about when and how they became infected. Individual infection (via the triatomine vector), congenital infection, oral infection (eg, contaminated food) and transfusion/transplantation all need to be considered. In these cases, none of those infected had a history of either transfusion or organ transplant.

The fact that the mother (I:2) of three of the CD-positive children (II:2, II:3, II:6) was seropositive raises the possibility of congenital transmission. Because maternal-fetal transmission rates are only 5% to 6% (16,17), it is unlikely that all three were vertically infected. However, the degree to which the parasite is controlled by the mother can have a powerful influence on the likelihood of transmission through...
the family was separated: the oldest siblings (II:2, II:3) moved north to La Serena, the mother (I:2) left for Santiago with her youngest daughter (II:7), and her other daughter (II:6) moved to Limache. Finally, in 1979, the entire family emigrated to the province of Quebec, where they currently reside.

Based on this history, it is plausible that the matriarch (I:2) and the three positive children (II:2, II:3, II:6) contracted CD by vectorial transmission in Limache, which was a small municipality in Valparaiso, one of the principal CD-endemic regions of Chile in the mid-20th century (19) (Figure 2). Housing quality is an important risk factor for triatomine infestation (eg, cane/thatch roofs, adobe/stone walls, poor ventilation) (20) and the family described their home as a rudimentary ‘country house’. However, these three children lived in Limache for only short periods of time (<3 years for II:2 and II:3 and six years for II:6), which narrows the time frame for vectorial transmission. Vectorial infection in La Serena is another possibility for II:2 and II:3, who lived in this small town for six years after the 1973 political crisis. In both of these smaller, rural communities, oral infection by contaminated food, juice or water may also have occurred. The only uninfected child in the second generation (II:7) was born in Concepción, which is below the southern limit of the geographical distribution of the triatomine vector in Chile (21), and lived only in Concepción and Santiago.

**Screening**

This family cluster illustrates the potential impact of screening programs for *T. cruzi* infection. Not only did it prevent the introduction of potentially contaminated blood into the blood pool, it also led to the diagnosis of CD in two additional family members (I:2, II:2). At the time of writing, the CBS selective screening program had identified 15 *T. cruzi* antibody-positive donors in the first three years of operation (12). Whether selective screening based on risk factors is sufficient to prevent the introduction of blood products contaminated with *T. cruzi* into the blood pool is a legitimate concern. Alternative and more comprehensive approaches include universal testing (every donor, every donation) and screening at the first interaction with blood services (so-called ‘screening in’) with subsequent rescreening based on new risks (eg, travel or residence in CD-endemic areas). A recent serosurvey involving >84,000 subjects who answered ‘no’ to all of the ‘risk questions’ found only one CD-positive individual (12,22), demonstrating that selective screening programs will only miss a very small number of cases in Canada. Vertical transmission of CD in nonendemic countries, such as Canada (11), Switzerland (23) and Spain (24), can occur and be undetected in the absence of selective prenatal screening. Although a screening program for pregnant women could theoretically identify candidates for serological screening, such a program would be cumbersome and very low yield. However, such a program would permit newborns of seropositive mothers to be tested at birth by PCR and/or microscopy of cord/venous blood (25) or by serology at eight to 10 months of age, after maternal antibodies are no longer present (26). CD can usually be successfully treated in infants (refer to Treatment section). Fortunately, none of the five children in the third generation of our family cluster were found to be CD positive.

**Evaluation of patients diagnosed with CD**

Subjects identified in screening programs (eg, blood bank, possibly prenatal care) first need to have the diagnosis confirmed using one or more reference tests (eg, TESA-ELISA, RIPA, PCR). Although there is no ‘gold standard’ assay, several such tests are available through the NRCP (www.nrcp.ca) in Canada or through other reference laboratories (eg, Centers for Disease Control and Prevention, www.cdc.gov). It is generally appropriate to screen the siblings and parents of any CD-positive subject as well as the children of infected mothers. A complete medical history and a physical examination should be performed, with a focus on signs and symptoms suggestive of cardiac or GI manifestations. Recommended testing includes a 12-lead ECG in all CD-positive patients (27). An echocardiogram
Multinational study, Benznidazole Evaluation for Interrupting Trypanosomiasis (BEENEFIT) (33). Results from this trial should be available sometime in 2015. Because toxicity with either benznidazole or nifurtimox can be severe and tends to increase in older individuals (30), the risk/benefit ratio of treatment worsens with age (27,31,32). As a result, there are no clear treatment guidelines for any of the 46- to 67-year-old adult patients in our family cluster, particularly for subjects I:2 and II:6, who have abnormal ECGs but normal echocardiograms. After discussion of the pros and cons of therapy, all four decided not to initiate treatment until the results of the BENEFIT trial are known. Although there was considerable optimism that posaconazole may be a less toxic alternative therapy, the results of a recent randomized, controlled trial versus benznidazole are not encouraging (34). New drugs with greater efficacy in the chronic phase of CD are urgently needed.

CONCLUSION

The present report describes an unusual family cluster of CD and illustrates the importance of screening ‘at-risk’ blood donors. Not only did this program prevent the entry of contaminated blood into the blood system, it also led to the diagnosis of CD in two other members of this family. Vertical transmission should always be considered when dealing with CD-positive mothers and, especially, pregnant women, because at-risk newborns and infants can be tested and successfully treated if found to be positive.

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