

Case report

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Typhoid fever: case report and literature review

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Abstract

Typhoid fever remains a major health problem worldwide, in contrast to Chile, where this disease is an isolated finding. Clinical presentation is varied, mainly presenting with fever, malaise, abdominal discomfort, and nonspecific symptoms often confused with other causes of febrile syndrome. We report a six-year-old, male patient presenting with fever of two weeks associated with gastrointestinal symptoms, malaise, hepatomegaly and elevated liver enzymes. Differential diagnoses were considered and a Widal reaction and two blood cultures were requested; both came back positive, confirming the diagnosis of typhoid fever caused by *Salmonella typhi*. Prior to diagnosis confirmation, empirical treatment was initiated with ceftriaxone and metronidazole, with partial response; then drug therapy was adjusted according to ciprofloxacin susceptibility testing with a favorable clinical response. We discuss diagnostic methods and treatment of enteric fever with special emphasis on typhoid fever.

Introduction

Enteric fever is a serious systemic infection caused by Gram negative bacteria; *Salmonella enterica* serotypetyp ϕ and *Salmonella enterica* serotype Paratyphi [1]. This disease is endemic to low- and middle-income countries. It is more common in the continents of Asia and Africa due to inadequate hygiene and the lack of safe drinking water. It is transmitted through the oral/fecal route [1],[2].

These microorganisms colonize the small intestine, invade the gastrointestinal mucosa and then spread to the liver, spleen and bone marrow [3]. The severity of the infection depends on the initial infective dose, virulence and the host immune response [4].

Both typhoid and paratyphoid fever tend to present acutely with similar clinical manifestations and incubation period of 5 to 12 days. Symptoms can range from a mild course with fever associated to general malaise, abdominal manifestations, roseola, sweating, headache, anorexia, cough, weakness, sore throat, dizziness and muscle pain, to, in some cases, neuropsychiatric manifestations

(between 5 and 10% of cases). Other findings include bradycardia, splenomegaly and hepatomegaly [1],[5]. Between the third and fourth week of infection 10-15% of patients may have gastrointestinal bleeding, intestinal perforation, encephalopathy and shock [6],[7]. Other reviews indicate complications such as disseminated intravascular coagulation, pneumonia, arthritis / arthralgia, altered mental status, hepatitis and meningitis [7].

If left untreated, typhoid fever has a mortality rate close to 10 or 15% reducing to one or two percent with adequate and timely antibiotic treatment [8]. Some reviews report that in children under four years lethality is 10 times higher than in older children [9].

By 2010, worldwide, typhoid fever caused about 21.7 million cases and 217,000 deaths; for paratyphoid fever the estimation was 5.4 million affected [1]. The greatest burden of disease was experienced by infants, children and adolescents in South Central and Southeast Asia. In view of the above, WHO recognizes this disease as a major public

health problem and recommends immunization with the Vi polysaccharide vaccine in high-risk areas [9]. Some studies recognize the importance of maintaining adequate monitoring of this disease, thus determining its geographical distribution and the most affected population in order to carry out targeted vaccination strategies [10].

However, Chile is a country that remains with low endemicity for this disease, with an incidence in 2015 of 0.4 cases per 100,000 inhabitants. Of the cases reported between 2007 and 2015, 87% were typhoid, 8% were paratyphoid fever and 4% paratyphoid unspecified. One of the regions with the lowest incidence is the seventh region of Maule where the data reported in the register of notifiable diseases show a cumulative rate of zero cases by 2015 [11].

Here we describe a case of typhoid fever without risk factors for this disease, treated at the San Juan de Dios Hospital, Curicó, Maule Region, Chile. The low incidence of this disease throughout the country and particularly in the region from which the patient comes, justifies the need to present this case. Although typhoid fever is an unusual and isolated diagnosis in Chilean hospitals today, it is necessary that health professionals maintain timely clinical suspicion, in order to make the corresponding study and give patients an effective and timely treatment, thereby decreasing the mortality associated with this disease.

Clinical case presentation

Six-year-old male patient, from the Maule Region. With a history of left inguinal hernia repair nine months ago, chicken pox three weeks ago and, as an important precedent, a trip to Lake Colbun 15 days before the start of the symptoms (one month before hospitalization). The patient does not refer having travelled abroad or any contact with a sick person.

He consults the emergency service for a history of fever up to 41° C of two weeks of evolution, which reduced partially with paracetamol. Fever was associated with abdominal pain, headache and repeated fetid watery stools without blood. The days before the consultation the patient presents anorexia, asthenia, nausea and vomiting. Initially he is handled with hydration, analgesia and antipyretics, without improvement, so hospitalization was decided.

Physical examination shows he was febrile, pale, with moderate dehydration, skin without lesions or lymphadenopathy. He had a distended abdomen, slightly depressible deep and painful to palpation, with liver dullness 5 to 6 cm below the costal margin, bowel sounds diminished and Blumberg sign absent. The rest of examination showed no findings. In this first instance a surgical cause was discarded.

Laboratory tests showed: CRP 14.68 mg/l, 25.6% hematocrit, hemoglobin 9.9 g/dL, mean corpuscular volume (MCV) 76.9 fl, mean corpuscular hemoglobin concentration (HCM) 27 pg, white blood cell count 11,000 cells/mm³ (segmented 77%, baciliform 20%), platelet

count 157,000 / mm³, erythrocyte sedimentation rate (VHS) 23 mm/hr, GOT (aspartate aminotransferase) 180.9 mg/dl, GPT (alanine aminotransferase) 67.8 mg/dl, LDH (lactate dehydrogenase) 497 U/L, albumin 2.4 g/dl, corrected calcium 8.8 mg/dl. Renal function, coagulation, venous gases and urine sediment were normal. Occult blood test in stools was positive. A search for rotavirus in depositions, urine and stool culture, and serial coproparasitological examination were also performed, all negative. In two consecutive blood cultures, awaiting final results, gram negative bacteria in abundant quantities are identified in the Gram stain. Based on the above, antibiotic treatment was initiated with ceftriaxone and metronidazole, at 48 hours of treatment partial response was obtained.

In view of the unspecific clinical picture and given the low response to antibiotics, the presence of intra-abdominal abscess was presumed, so an abdominal ultrasound is performed showing a moderate hepatomegaly. An abdominal computed tomography with contrast shows bilateral nephritis, enteritis of jejunum and ileum associated to right-colitis, periportal edema, liver and perirenal mass, a small amount of free fluid in the abdomen and pelvis, and bibasal pleural effusion. With these data, the patient is evaluated by pediatric surgery where the presence of an abscess is finally discarded.

During the clinical picture, enteric fever is suspected despite its low prevalence in this country. A Widal reaction Eberth O and H was requested which was reactive in 1:256 dilution, paratyphi A and B negative. The two blood cultures indicated at admission were finally positive for Salmonella typhi and sensible to ciprofloxacin and cephalosporin. With lab results typhoid fever from Salmonella typhi was finally diagnosed and antibiotic treatment was adjusted according to sensitivity showed in antibiogram. In this case we added Ciprofloxacin, which is among the first-line antibiotics for the management of this condition. After two days with this scheme the patient progressed satisfactorily.

Discussion

Prolonged febrile syndrome is a common presentation of various diseases in children, with a broad spectrum of possible etiologies, from some very common to some uncommon. This, according to the area of origin of the patients, such is the case of typhoid fever endemic in many regions of the world but rare in Chile due to better sanitary conditions in the country. Being Salmonella typhi an infection disease difficult to diagnose in children because of the low specificity of symptoms, it tends to be confused with malaria, dengue, flu and other febrile illnesses in countries where such diseases are endemic [12].

In low prevalence countries, such as the case above, the differential diagnoses correspond to the most frequent causes of fever without focus, of short and intermediate duration. For this reason, in first instance viral infections, acute abdominal processes, both medical and surgical, including bacterial enterocolitis, acute appendicitis, and so on were ruled out. But as the febrile illness persisted, the possibility of an intra-abdominal abscess, a diagnosis that

was excluded by imaging tests, was investigated. If even with a thorough study, there were no accurate diagnosis, efforts should be geared to rule out the presence of atypical pathogens, excluding bacterial endocarditis, rickettsial diseases, tuberculosis, brucellosis, lymphoproliferative diseases, among others. But given that a definitive diagnosis with the results of blood cultures was obtained, it was not necessary to investigate other diagnostic possibilities beyond those presented, since the diagnostic confirmation requires the isolation of *Salmonella typhi* [13].

The cornerstone in the diagnosis is blood microbiological culture, however, the greatest degree of sensitivity occurs during the first week. During the rest of the clinical picture, sensitivity is between 40 and 60%, but maintains a specificity of nearly 100%. The bone marrow culture has shown a sensitivity greater than 80%, independent of previous use of antimicrobials and the week in which this is done, but it is technically difficult and invasive, which limits its use. Other cultures may be the feces, urine and duodenal contents but these require more cautious interpretation because both can be positive in chronic carriers found in acute stage [5]. In our case the patient had two weeks of clinical manifestations, with two positive serial blood cultures for this agent so there was no need for more invasive procedures.

Serodiagnosis of typhoid fever, can be determined with the Widal reaction, which establishes the presence of antibodies against O and H antigen for *Salmonella typhi*. This reaction tends to overdiagnose the disease because of the numerous cross-reactions it has. In addition, it is necessary to consider that a negative Widal reaction does not exclude the diagnosis in a clinical picture compatible with the disease and that for its interpretation it is necessary to know the prevalence of the area, so it is not recommended its use in Chile [11],[14].

ELISA test, used to measure antilipopolysaccharides antibodies and anti-flagella antibodies is more sensitive than the Widal reaction, it is still limited for its low specificity in endemic areas for this disease [15].

Rapid diagnostic tests can detect IgM antibodies in blood type antigens against salmonella, suggestive of current or recent infection, and IgG indicates previous exposure. In cases of typhoid fever with positive blood culture, TUBEX has a sensitivity and specificity of 56-100% and 58-100%, respectively; Typhidot with a sensitivity and specificity of 47-98% and 73-100%, respectively, Typhidot-M has sensitivity and specificity of 47 to 98% and 65 to 93% respectively. The sensitivity of these tests in patients with suspected typhoid fever but with negative blood cultures can vary from 8 to 100%, so they are open to investigator bias [5].

Some reviews show that based real-time PCR assays have a sensitivity of 100% in patients with positive bone marrow cultures, it is recommended as a suitable test in places where it is not possible to do routinely blood cultures [16].

An immunodiagnostic test for typhoid and paratyphoid fever (TPTEST), based on the use of secretions antibodies

from peripheral blood lymphocytes, had a sensitivity of 100% compared to the blood culture and specificity ranging between 78 and 97% (95% CI 73-100) in endemic regions, with highlights that this is inexpensive, uses small volumes of blood and becomes negative in periods of convalescence [17].

Therapy and optimal duration of treatment for this condition has not been determined. According to data obtained from Cochrane 2013, in the context of multiple resistance to first-line drugs (amoxicillin / ampicillin, cotrimoxazole and chloramphenicol), fluoroquinolones are considered of choice, because it has been shown that they have lower clinical failure compared with cephalosporins [18]. However, the increase in resistance of the former in endemic areas, has opted for management with third-generation cephalosporins such as ceftriaxone and azithromycin parenteral pathway [19]. As it is used in combination with ciprofloxacin ceftriaxone. A study in Chennai, India, in 2009, shows a sensitivity of 86% to chloramphenicol, ampicillin, cotrimoxazole 84% and 88%. It also showed a higher sensitivity to cephalosporins, followed by ciprofloxacin [20]. As for the duration of treatment 5 to 10 days it is recommended to fluoroquinolones or azithromycin, and 7 to 14 days for beta-lactam [19].

Typhoid fever due to multiresistant strains of *Salmonella typhi*, that is, resistant to all three first-line antibiotics (chloramphenicol, ampicillin and cotrimoxazole) - has been associated with more severe disease, with higher rates of complications and mortality, especially in children under two years. Furthermore, in *Salmonella typhi* multiresistant infections, the percentage of chronic carriers after antibiotic treatment is ten times greater compared to cases that were due to susceptible strains [9]. In our case we had a strain sensitive to fluoroquinolones and cephalosporins, according to antibiogram, so he could be treated effectively with a drug of choice for this condition.

Conclusions

Typhoid fever is a disease of high prevalence in Asia and Latin America, but is unusual in Chile. This case reminds us of the importance of keeping typhoid fever in the differential diagnosis of febrile syndromes. That is, one should not forget the possibility of a febrile syndrome corresponds to a case of typhoid fever, because although uncommon in Chile -due to improvements in the sanitary conditions of the country- there is still the possibility of encountering this condition.

Despite worldwide efforts to maintain adequate surveillance and improve diagnostic methods, it remains a difficult picture to recognize because of the low sensitivity of both clinical and laboratory examinations. Taking it into account allows the clinician to resort to alternative diagnostic methods in case of therapeutic failure, because if it is not defined right and timely for proper antibiotic treatment, it can lead to a high mortality rate. Finally, it is important to review and investigate similar literature, to maintain the perception of this disease active.

Notes

From the editor

The authors originally submitted this article in Spanish and subsequently translated it into English. The *Journal* has not copyedited this version.

Ethical aspects

Informed consent requested by *Medwave*, has been signed by the patient's mother and a copy was sent to the *Journal* editorial board.

Conflicts of interest

The authors completed the ICMJE declaration of conflicts of interest and declare they have not received funding for the completion of the report; have no financial relationships with organizations that may have interests in the article published in the last three years; and have no other relationships or activities that could influence the published article. Forms can be requested by contacting the responsible author or editorial direction of the *Journal*.

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