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Complications of Gastroenteritis By Typhoid Fever in Amazonia: Clinical Cases Genetic Evaluation from Intestinal Drilling, Pneumonia and Cholestatic Hepatitis

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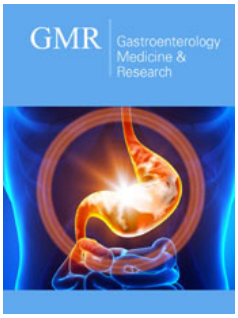

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Abstract

Typhoid fever is a systemic bacterial disease caused by *Salmonella enterica* serotype Typhi, manifested by prolonged fever accompanied by intestinal disorders, which in some cases may progress to intestinal perforation, and can also cause pneumonia and cholestatic hepatitis. The virulence of *Salmonella* Typhi is highly complex, involving the expression of numerous genes, which encode toxins, adhesins, invasions or other virulence factors. In the present work, the bacterial isolate from three clinical cases of typhoid fever complications (intestinal perforation, pneumonia and cholestatic hepatitis) were tested for six virulence genes (*invA, viAB, prt, tcf, tyv* and *H-d*). The samples showed the same results in the PCR identifying the agent as *Salmonella* Typhi, without the presence of other non-Typhi *Salmonella*, being observed the existence of high genetic similarity between the samples of the analyzed clinical cases.

Keywords: *Salmonella* Typhi; Virulence genes; Polymerase chain reaction (PCR)

Introduction

Typhoid fever is a systemic disease caused by *Salmonella enterica* serotype Typhi, characterized by high fever accompanied by intestinal disorders, whose transmission occurs through the consumption of contaminated water and food [1,2]. The method used for the diagnosis is culture, which can result in false negatives due to previous use of antibiotics. Failure to diagnose the outcome makes therapeutic conduct unfeasible, constituting an aggravating factor in the clinic than some cases. One way around this problem is to use assays based on the amplification of nucleic acids [3,4]. Typhoid fever remains one of the most important infectious diseases in the world, which has seen little decrease in mortality rates since the 1990s [5]. Countries in East and Southeast Asia, Africa, the Caribbean, Central and South America currently suffer from this public health problem [6]. The World Health Organization (WHO) estimates that there are 11 to 20 million new cases in the world and approximately 128,000 to 161,000 deaths each year [7]. In Brazil, between 2001 and 2019, 1,745 cases of typhoid fever were confirmed, the Brazilian Amazon, although it represents 59% of the Brazilian territory, but with the lowest population density, 12.83% of the total population, reported the largest number of cases at all parents with 1,491 (85.44% of the national total) [8]. Thus, the Evandro Chagas Institute (IEC) invests in the program aimed at the surveillance of gastroenteric diseases and their complications with a focus on laboratory diagnosis of patients with suspected typhoid fever from all over the Brazilian Amazon [9].

Methods

Three *Salmonella* Typhi bacterial isolates from blood culture and coproculture of patients with intestinal perforation, pneumonia and cholestatic hepatitis were evaluated, available at the Bacteriology and Mycology Section of the Evandro Chagas Institute (IEC). To identify the *Salmonella* species and its genetic profile, six virulence genes *invA, viAB, prt, tcf, tyv* and *H-d* were analyzed [3,10,11]. The DNA of the bacterial isolates was extracted using the boiling and freezing technique [12]. Each set of primers (1.25mM) was incubated in an amplification reaction with a final volume of 25µL, containing 20ng of DNA, 10Mm Tris-HCl, pH 8.5,

50mMKCl, 1.5/µMMgCl$_2$, 1.25mM of each dNTP and 0.5 units of Taq DNA polymerase Platinum (Invitrogen), incubated in an automatic gradient thermocycler model Vereti™ 96-Well Thermal Cycler (Applied Biosystems-US), with program: four minutes at 95ºC, thirty-five one minute cycles at 95ºC, one minute at 60ºC and one minute at 72ºC, final cycle of seven minutes at 72ºC. The product was visualized on an agarose gel (2%) using a 1Kb molecular weight marker, together with the positive control (strain S57) and negatives.

Results

As result, it was observed that in the three clinical cases analyzed, all the investigated genes (*invA, viAB, prt, tcf, tyv* and *H-d*.) were amplified, characterizing the presence of *Salmonella* Typhi, with no other species or serogroup of *Salmonella*. There were no variations in the molecular weight of the amplicons, which demonstrated genetic similarity between all samples surveyed (Figure 1). When comparing the three clinical cases, there was also no variation between samples, with all of them showing the same amplification pattern in relation to the studied genes.

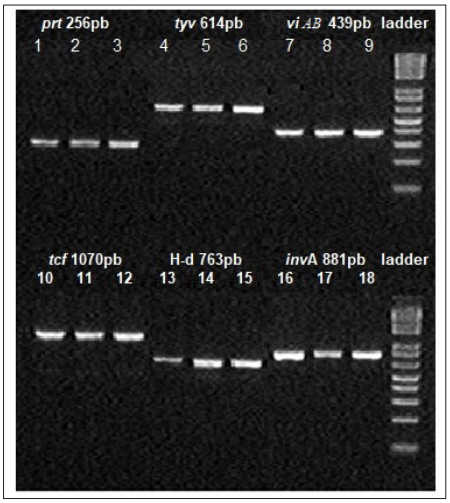

Figure 1: Electrophoresis in 2% agarose gel for visualization of the amplification product using the primers *prt, tyv, viAB, tcf, H-d and invA*: 1, 4, 7, 10, 13 and 16 - intestinal drilling; 2, 5, 8, 11, 14 and 17 - pneumonia; 3, 6, 9, 12, 15 and 18 - cholestatic hepatites, *Ladder* 1Kb. Source: IEC Collection.

Discussion

Complications of typhoid fever are rare in immunocompetent patients, being more frequent in patients with immunodeficiency syndromes, immunosuppressed transplant recipients or even in children [13-15]. The patient with intestinal perforation analyzed in the present study was seen at the Evandro Chagas Institute and diagnosed with *Salmonella* Typhi by the classic methods of coproculture, however the evaluation of the presence of the invA, viAB, prt, tcf, tyv and H-d genes was necessary due to the existence of other endemic agents that cause gastroenteritis in the region and the existence of 2500 *salmonella* serotypes and there are no studies on the distribution of these serotypes in the Brazilian Amazon. However, the results showed that there was no other agent involved and confirmed *Salmonella* Typhi as the causative agent. The data for virulence genes are important since the pathogenesis of the disease is related not only to the infectious bacterial load, estimated at 10^6 to 10^9 ingested bacteria, but also to the virulence of the strain and the host's immune response, which can facilitate or hinder the evolution of the disease to more severe cases such as intestinal perforation [16]. Thus, often associated with gastrointestinal disorders, *Salmonella* can cause pneumonia and cholestatic hepatitis in addition to intestinal perforation. Although historically associated with immunodeficiency [13,14], pulmonary cases of *Salmonellas* are also described in immunocompetent patients, who can progress to septic shock and multiple organ failure. In these cases, pneumonia can be caused only by Salmonella or in association with other bacteria or even viruses. However, in the existing studies the Salmonellas found are often *Salmonella* Enteritidis, *Salmonella* enterica serotype Choleraesuis, with rare cases associated with *Salmonella* Typhi. Unlike what was observed in the present study, which identified only *Salmonella* Typhi as the causative agent, no association with other bacterial or viral agents was observed. At this point, analyzes by molecular methods were fundamental for the precise identification of the agent involved, since in the Amazon it is common to have asymptomatic cases of typhoid fever that can evolve to a pulmonary complication easily confused with other conditions existing in the region [13-15,17,18].

Thus, the interaction of *Salmonella* in cases of gastrointestinal disorders, intestinal perforation, pneumonia, meningitis, vertebral osteomyelitis, septic shock and multiple organ failure seems to be conclusive, but much has been discussed about *Salmonella*, especially *Salmonella* Typhi in hepatitis. Thus, studies have linked the occurrence of hepatitis to typhoid fever [18-21]. Although liver cases of typhoid fever can be concomitant with Hepatitis A, there are cases described for cholestatic hepatitis negative for Hepatitis A, B and C [20,21]. Similar to what was observed in the case analyzed by us, which was not observed an association of other agents to the case of cholestatic hepatitis, besides the identification of *Salmonella* Typhi. Additionally, it was important to note the existence of high genetic similarity between the *Salmonella* Typhi samples from the three analyzed clinical cases, indicating that although they may be representatives of the same circulating clone, the strains that are generally responsible for typhoid fever, can cause important changes in the host organism without changing the profile of virulence genes frequently involved in classic typhoid fever, and that the analysis of a large number of cases is necessary to unravel the mechanisms that may be involved in complications due to *Salmonella* infection, in particular *Salmonella* Typhi.

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