Human granulocytic Anaplasmosis (HGA)

Subjects: Pathology

Contributor: Carolina G. Sosa-Gutierrez

Human granulocytic Anaplasmosis (HGA), is a tick-borne infectious disease transmitted by ticks, resulting in acute feverish episodes. The etiological agent is the bacteria Anaplasma phagocytophilum; which is spread by ticks of the genus Ixodes spp. to complete its life cycle.

Keywords: Anaplasma phagocytophilum ; zoonosis ; humans ; serology ; molecular

1. Introduction

Human Granulocytic Anaplasmosis (HGA) is an infectious disease transmitted by ticks. Its manifestation results in acute feverish episodes and the etiological agent causing this is the bacterium *Anaplasma phagocytophilum*. *A phagocytophilum* completes its life-cycle through ticks of the genus *Ixodes spp*. and the principal reservoir for *A. phagocytophilum* is the white-footed mouse, *Peromyscus leucopus* [1]. Other mammals, such as “white-tailed deer” *Odocoileus virginianus,* may also carry the bacterium and serve as long-term asymptomatic hosts [2]. Other mammals occur, such as squirrels, voles, wood rats, roe deer, deer, cats, dogs, horses, ruminants and other sylvatic species that serve as reservoirs of diseases [3][4]. The distribution of this disease is related directly to the distribution of the vector. The infection has been reported globally [5].

Anaplasma phagocytophilum is an obligate intracellular and Gram negative bacterium, with a specific tropism towards leukocytes and platelets. These bacteria thrive and multiply within the cytoplasmic vacuoles of the host’s cells, thereby evading neutrophils and the antimicrobial functions of the host’s immune system. The infection is acquired through tick bites. Once in the host it disseminates to the bone marrow and the spleen, provoking within human patients a decrease in the elemental functions of these [2][4][5]. Symptoms are manifested within 5–14 days after the bite from an infected tick and generally the clinical manifestations vary from mild to severe and may include fever (92–100%), general discomfort (97%), myalgia (77%), headache (82%), and in less than 50% of cases vomiting, nausea, diarrhea and coughing. Effects to the central nervous system is rare [6]. Severe manifestation of the diseases may result in labored breathing, septic shock, multi-organ failure and rhabdomyolysis, as well as opportunistic infections [7][8]. However, there have been reports of peripheral neuropathy, thromboembolic pathologies, hemorrhagic manifestations, pancreatitis and acute renal failure [6].

Possible factors affecting the severity of Anaplasmosis manifestation may include being elderly, immunosuppressed, medical conditions such as diabetes and a delay in positive diagnosis and treatment of the disease. Fatality rates are greater for persons over 70 years of age and those with immunosuppression [6][8]. The majority of cases have been reported in the United States of America; nevertheless, reports containing serological evidence in Latin America, including Mexico, exist, particularly in a patient engaged in high risk activity [9]. A positive diagnosis may be confirmed through various methods, such as serological tests and examination of blood smears, which would reveal the presence of morulas within the granulocytes, DNA detection through PCR testing, bacterial detection through the examination of histological samples (such as those from bone marrow, spleen, lymphatic nodes, liver, or pulmonary tissues), or through culture isolation [4][6]. Detection through PCR testing of DNA is sensitive and specific for the diagnosis of acute anaplasmosis [9][10].

Tick-borne diseases are a serious public health concern, as the reported incidence of tickborne diseases has increased during the past decade and has erupted in areas not previously reported such as Ecuador, Chile and Mexico [11][12][13]. These have caused serious illness and death in children and adults, regardless of the availability of adequate treatment, such as early diagnosis [6]. Presently, Mexico only recognizes *Rickettsia rickettsii*, which has also been the cause of the latest outbreaks in the country since 2009, resulting in fatalities in 12% of those infected [13][14]. Throughout the northern part of the country, concerted efforts are being made to better understand the depth of this public safety problem [1][11]. There is a lack of information regarding how other bacteria or the overlap of other bacteria affect the clinical manifestations of the infection. The presence of the suitable vector as well as known reservoirs in the sylvatic life cycle of the bacterium has been reported in Mexico [9][11][15][16][17]. Coupled with the quantity of children, elderly adults and middle-

aged adults presenting clinical symptoms (fever, headache, nausea, vomiting, abdominal discomfort, diarrhea, arthralgia, myalgia, hepato-splenomegaly, gingivohemorraging, petechial and increase transaminase levels, among some) [2]; are suggestive for hemorrhagic syndromes such as Zika, Chikungunya, classic and hemorrhagic Dengue, and of course tick-borne diseases.

2. Patients Infected with Anaplasma phagocytophilum

Human granulocytic Anaplasmosis (HGA), is a tick-borne infectious disease transmitted by ticks, resulting in acute feverish episodes. The etiological agent is the bacteria *Anaplasma phagocytophilum*; which is spread by ticks of the genus *Ixodes spp*. to complete its life cycle. In Mexico, there is only one case report. The primary challenge is understanding how other bacteria affect or overlap with the clinical manifestation of the disease. Sample collection occurred over the period September 2017 through October 2019. Blood samples from human subjects were obtained immediately after they signed consent forms. We analyzed for the presence for *A. phagocytophilum* by serological (IFA IgG two times) and PCR targeting *16SrRNA* and *groEL* genes, followed by DNA sequencing. All patients with a history of travel abroad were dismissed for this project. In total, 1924 patients participated and of these, 1014 samples across the country were analyzed. Of these, 85 (8.38%) had IFA results that ranged from 1:384 to 1:896. Of the positive samples, 7.10% were used for PCR. Significant clinical manifestations included: dizziness, nausea, petechial, epistaxis, enlarged liver and/or spleen and thrombocytopenia. Hospitalization of at least 1.5 days was necessary for 3.2% of patients. None of the cases analyzed were lethal. This is the first clinical manifestations along with serological test results and molecular analysis confirmed the presence of *A. phagocytophilum* resulting in HGA in patients from Mexico. Health institutions and medical practitioners in general should include diagnostic testing for HGA among high risk populations and should recognize it as a vector-borne emerging infectious disease in Mexico.

In Mexico, the presence of *A. phagocytophilum* in the competent vector, reservoirs of the domestic and wild cycle, such as dogs, mice and opposums, for which it was essential to carry out a search for possible infected patients, as well as the characterization of their clinical manifestations and possible lesions of HGA infection, is why it is important to answer the question of the existence of possible cases, their symptoms, and epidemiological findings. These results further support and provide evidence of the existence of human infection of *Anaplasma phagocytophilum* in Mexico, further confirming previous suggestive serological and molecular tests [1][9][11], these indicated the presence of the bacteria throughout the vector's environment, as well as reservoirs as dogs and opossums; and accidental human hosts causative of the disease [15][16][17][18][19].

The frequency of infection obtained through the IFA technique is low compared to the United States, where average samples consist of 6.3 cases per million habitants [6][20][21] and Canada [22]. This is consistent, since obligatory records of incidence must be maintained, whereas Mexico has no precedents of this disease with the exception of a case studies [9], and a vector and domestic and wildlife reservoirs reported such a dogs and oposums [21][22][23][24][25]. Employing IFA with antibodies IgG as one of the methods to diagnose the disease may result in low sensitivity for patients in an acute phase. Evidence exists that the antibodies for A. phagocytophilum, may remain elevated up to 4 years after the initial diagnosis. However, only 24.71% of the patients who tested positive consented to a second sampling. All of these resulted in levels 6 to 12 times greater of those obtained from the previous sample.

Of the 85 patients who tested positive, all reported that they had not travelled abroad, this supports that the disease was acquired in Mexico. Only 7.10% of the patients tested positive using PCR. The sensitivity, once the infection is acute, may be low but the specificity of this technique is irrevocable since it demonstrates 100% homology in comparison to other strains already described as being tested for in these patients. It has been shown that *A. phagocytophilum* can circulate in different host tissues and vectors; similar to the fauna found in Mexico. Although human cases have been identified in an ecotype, it is not ruled out that this may increase due to the expansion of the vector [23]. Clinical manifestation is similar to those reported by characteristic patients with the exception of the presence of rashes, subjects from this study reported a 10% incidence of these in comparison to the average, which is lower than 7%. No abnormalities were detected during the sampling of the cerebrospinal fluid, excepting protein levels. No cases of fatality occurred, in comparison with the reported 0.3 fatality in persons over the age of 60. Nevertheless, it is important to note that the average age for patients who tested positive was 52.6 years of age. Despite the fact that patients responded well to the treatment, which consisted of doxycycline, it should be pointed out that ticks transmit other pathogens such as *Babesia spp*. *Borrelia spp*. and *Ehrlichia chaffeensis*, thus co-infections may occur. Cases of *B. burgdorferi* have been reported from the northern part of the country, with some neurological pediatric patients, and one fatality by *E. chaffeensis* in a patient from central Mexico [15][24][26]. In the United States, coinfections are reported in 10% of cases across the country and 6.8% seropositive samples for antibodies against at least one pathogen in Northern California, a western border with Mexico [6][27][28].

3. Conclusion

It is known that *A. phagocytophilum* is a bacterium that is difficult to cultivate in liquid media, as well as the prolonged time required, approximately 1.2 months. Understanding the dynamics of disease transmission in the human–domestic and wildlife cycle in a national serological study is necessary, in which a secondary sample of patients is obtained in conjunction with a risk level map.

References

1. Sosa-Gutierrez, C.G.; Vargas, M.; Torres, J.; Gordillo-Perez, M.G. Tick-borne rickettsial pathogens in rodents from Mexico. J. Biomed. Sci. Eng. 2014, 7, 884–889.
2. Dumler, J.S.; Choi, K.S.; Garcia, J.C.; Barat, N.S.; Scorpio, D.G.; Garyu, J.W.; Bakken, J.S. Human Granulocytic Anaplasmosis and Anaplasma phagocytophilum. Emerg. Infect. Dis. 2005, 11, 1828–1834.
3. Nicholson, W.L.; Allen, K.E.; McQuiston, J.H.; Breitschwerdt, E.B.; Little, S.E. The increasing recognition of rickettsial pathogen in dogs and people. Trends Parasitol. 2010, 26, 205–212.
4. Guzman, N.; Beidas, S.O. Anaplasma phagocytophilum (Anaplasmosis). In StatPearls; StatPearls Publishing: Treasure Island, FL, USA, 2019. Available online: (accessed on 1 February 2021).
5. Bakken, J.S.; Dumler, J.S. Human granulocytic anaplasmosis. Infect. Dis. Clin. N. Am. 2015, 29, 341–355.
6. Biggs, H.M.; Behravesh, C.B.; Bradley, K.K.; Dahlgren, F.S.; Drexler, N.A.; Dumler, J.S.; Traeger, M.S. Diagnosis and Management of Tickborne Rickettsial Diseases: Rocky Mountain Spotted Fever and Other Spotted Fever Group Rickettsioses, Ehrlichioses, and Anaplasmosis—United States. MMWR Recomm. Rep. 2016, 65, 1–44.
7. Graf, P.C.; Chretien, D.L.; Ung, L.; Gaydos, J.C.; Richards, A.L. Prevalence of seropositivity to Spotted fever group Rickettsiae and Anaplasma phagocytophilum in a agrge, demographically diverse US sample. Clin. Infect. Dis. 2008, 46, 70–77.
8. Thomas, R.J.; Dumler, J.S.; Carlyon, J.A. Current management of human granulocytic anaplasmosis, human monocytic ehrlichiosis and Ehrlichia ewingii Ehrlichiosis. Expert Rev. Anti-Infect. 2009, 7, 709–722.
9. Sosa-Gutierrez, C.G.; Cervcantes-Castillo, M.A. First case report of Human Granulocytic Anaplasmosis in Mexico with serological and molecular evidence. Biomed. J. Sci. Tech. Res. 2018, 3, 304–306.
10. Liz, J.S.; Sumner, J.W.; Pfister, K.; Brossard, M. PCR detection and serological evidence of granulocytic ehrlichial infection in roe deer (Capreolus capreolus) and chamois (Rupicapra rupicapra). J. Clin. Microbiol. 2002, 40, 892–897.
11. Sosa-Gutierrez, C.G.; Vargas-Sandoval, M.; Torres, J.; Gordillo-Pérez, G. Tick-borne rickettsial pathogens in questing ticks, removed from humans and animals in Mexico. J. Vet. Sci. 2016, 17, 353–360.
12. Maggi, R.G.; Krämer, F. A review on the occurrence of companion vector-borne diseases in pet animals in Latin America. Parasit Vectors 2019, 12, 145.
13. Álvarez-Hernández, G.; Roldán, J.F.G.; Milan, N.S.H.; Lash, R.R.; Behravesh, C.B.; Paddock, C.D. Rocky Mountain spotted fever in Mexico: Past, present, and future. Lancet Infect. Dis. 2017, 17, e189–e196.
14. Álvarez-Hernández, G.; Candia-Plata, M.; Delgado-de la Mora, J.; Acuña-Meléndrez, N.; Vargas-Ortega, A.; Licona-Enríquez, J. Fiebre maculosa de las Montañas Rocosas en niños y adolescentes mexicanos: Cuadro clínico y factores de mortalidad. Salud Pública México 2016, 58, 385–392. (In Spanish)
15. Feria-Arroyo, T.P.; Castro-Arellano, I.; Gordillo-Perez, G.; Cavazos, A.L.; Vargas-Sandoval, M.; Grover, A.; Esteve-Gassent, M.D. Implications of climate change on the distribution of the tick vector Ixodes scapularis and risk for Lyme disease in the Texas-Mexico transboundary region. Parasites Vectors 2014, 7, 199.
16. Vargas-sandoval, M.; Priego-Santander, A.G.; Larrazábal, A.; Sosa-Gutierrez, C.G.; Lara-Chavez, M.B.; Avila-Val, T. Potential sepecies distribution and richness of Ixodidae ticks associated with wild vertebrates from Michoacan, Mexico. J. Geogr. Inf. Syst. 2014, 6, 2014.
17. Illoldi-Rangel, P.; Rivaldi, C.L.; Sissel, B.; Trout Fryxell, R.; Gordillo-Pérez, G.; Rodríguez-Moreno, A.; Sarkar, S. Species distribution models and ecological suitability analysis for potential tick vectors of lyme disease in Mexico. J. Trop. Med. 2012, 2012, 959101.
18. Frans, O.L.; Wilhelmsson, P.; Sjöwall, J.; Jonsson-Henningsson, A.; Nordberg, M.; Jørgensen, C.S.; Krogfelt, K.A.; Forsberg, P.; Lindgren, P.E. Emerging tick-borne pathogens in the Nordic countries: A clinical and laboratory follow-up study of high-risk tick-bitten individuals. Ticks Tick-Borne Dis. 2020, 11, 101303.

19. Carpi, G.; Bertolotti, L.; Pecchioli, E.; Cagnacci, F.; Rizzoli, A. Anaplasma phagocytophilum groEL gene heterogeneity in Ixodes ricinus larvae feeding on roe deer in Northeastern Italy. Vector Borne Zoonotic Dis. 2009, 9, 179–184.
20. Dewage, B.G.; Little, S.; Payton, M.; Beall, M.; Braff, J.; Szlosek, D.; Knupp, A. Trends in canine seroprevalence to Borrelia burgdorferi and Anaplasma spp. in the eastern USA, 2010–2017. Parasites Vectors 2019, 12, 476.
21. Pascoe, E.L.; Stephenson, N.; Abigana, A.; Clifford, D.; Gabriel, M.; Wengert, G.; Brown, R.; Higley, M.; Bloch, E.M.; Foley, J.E. Human Seroprevalence of Tick-Borne Anaplasma phagocytophilum, Borrelia burgdorferi, and Rickettsia Species in Northern California. Vector Borne Zoonotic Dis. 2019.
22. Nelder, M.P.; Russell, C.B.; Lindsay, R.; Dibernardo, A.; Brandon, N.C.; Pritchard, J.; Johnson, S.; Cronin, K.; Patel, S.N. Recent Emergence of Anaplasma phagocytophilum in Ontario, Canada: Early Serological and Entomological Indicators. Am. J. Trop. Med. Hyg. 2019, 1–10.
23. Jahfari, S.; Coipan, E.C.; Fonville, M.; van Leeuwen, A.D.; Hengeveld, P.; Heylen, D.; Sprong, H. Circulation of four Anaplasma phagocytophilum ecotypes in Europe. Parasites Vector 2014, 7, 365.
24. Sosa-Gutierrez, C.G.; Solorzano-Santos, F.; Walker, D.H.; Torres, J.; Serrano, C.A.; Gordillo-Perez, G. Fatal Monocytic Ehrlichiosis in Woman, Mexico, 2013. Emerg. Infect. Dis. 2016, 22, 871–874.
25. Gordillo-Perez, G.; Torres, J.; Solórzano-Santos, F.; De Martino, S.; Lipsker, D.; Velazquez, E.; Jaulhac, B. Borrelia burgdorferi infection and cutaneous Lyme disease, Mexico. Emerg. Infect. Dis. 2007, 13, 1556–1558.
26. Ismail, N.; Bloch, K.C.; McBride, J.W. Human ehrlichiosis and anaplasmosis. Clin. Lab. Med. 2010, 30, 261–292.
27. Rojero-Vazquez, E.; Gordillo-Perez, G.; Weber, M. Infection of Anaplasma phagocytophilum and Ehrlichia spp. In Opposums and dogs in Campeche, Mexico: The role of tick infestation. Front. Ecol. Evol 2017, 5, 161.
28. Movilla, R.; Garcia, C.; Siebert, S.; Roura, X. Countrywide serological evaluation of canine prevalence for Anaplasma spp., Borrelia burgdorferi (sensu lato), Dirofilaria immitis and Ehrlichia canis in Mexico. Parasites Vectors 2016, 9, 421.