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Ehrlichiosis y anaplasmosis humanas en América

(Human Ehrlichiosis and Anaplasmosis in America)

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Resumen

Se realiza una descripción de los agentes de *Ehrlichia* y *Anaplasma* que han sido vinculados con la generación de enfermedad los seres humanos, dando especial énfasis *Ehrlichia chaffeensis*, *Anaplasma phagocytophilum* y *Ehrlichia canis*. Se describe además, el cuadro clínico relacionado con cada agente, su correspondiente diagnóstico y tratamiento.

Descriptores: Ehrlichiosis, anaplasmosis, humanos, América

Abstract

A description of *Ehrlichia* and *Anaplasma* agents that have been linked to human disease is presented. A particular emphasis is given to *Ehrlichia chaffeensis*, *Anaplasma phagocytophilum*, and *Ehrlichia canis*. The clinical features associated with each agent, as well as the corresponding diagnosis and treatment are also described.

Keywords: Ehrlichiosis, anaplasmosis, humans, America

Ehrlichia and *Anaplasma* are two major genera in the family Anaplasmataceae, order Rickettsiales. While infections by these genera have been well known in animals for many years, infections by Anaplasmataceae species have only been documented in humans since the mid-1980s. Thus, the focus of this mini-review is on ehrlichiosis and anaplasmosis in humans.

Since the first descriptions, human infections caused by new species, including *Ehrlichia chaffeensis* (cause of HME or human monocytic ehrlichiosis),[1] *Ehrlichia ewingii*,[2] an *Ehrlichia muris*-like agent (EMLA),[3] the Panola Mountain Ehrlichia (PME) which has similarities to *Ehrlichia ruminantium*,[4] and *Anaplasma phagocytophilum* (cause of human granulocytic anaplasmosis-HGA) have been identified in the Americas.[5,6] The only evidence of human infections by any of these species in Central or South America is limited to the cultivation of *E. canis* from an asymptomatic person in Venezuela,[7] several cases of *E. canis* infection in symptomatic patients in Venezuela,[8] a single case of *E. chaffeensis* infection in a Venezuelan child,[9] or to limited serologic suspicion based on high antibody titers in seroprevalence studies or seroconversions in individual patients. All species in these genera are transmitted to their vertebrate hosts by tick bites, including *Amblyomma americanum* in the US for *E. chaffeensis*, *E. ewingii* and the PME; EMLA and *A. phagocytophilum* are transmitted by *Ixodes scapularis* in the US. It is speculated that *E. canis* is transmitted to humans in Venezuela by *Rhipicephalus sanguineus* ticks,[10] the known vector for dogs.

Since first recognized and data was collected in the US, the CDC has recorded 8,404 cases of HME and 10,181 cases of HGA. In the US, the geographic location for HME and *E. ewingii* infection largely correspond to areas of *A. americanum* abundance and to areas of *I. scapularis* abundance for HGA and EMLA infection.[11] Whereas *E. canis* and *R. sanguineus* ticks are widely distributed throughout all of North, South and Central America, human infection has only been recognized among 7 individuals so far, and only in a single location in Lara State, Venezuela.[7,8] Although *A. phagocytophilum* has been identified

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Table. Serologic, culture, blood smear, and PCR evidence of ehrlichiosis or anaplasmosis in Latin America

Country	Year	N	Population or patient presentation	*Serological tests*			Final report	Dx based on	Notes	PMID
				E. chaffeensis	*E. canis*	VHE5				
Argentina	1999	105	healthy subjects	15	nd6	nd	*E. chaffeensis*[1]	serology		10463693
Brazil	2004	?	suspected Brazilian spotted fever	2	nd	nd	*E. chaffeensis*[2]	serology		15476059
Brazil	2005	437	healthy subjects	46	nd	nd	*E. chaffeensis*[1]	serology		16444416
Brazil	2006	771	fever	9	nd	nd	*E. chaffeensis*[3]	serology		16767308
Chile	2003	19	healthy subjects exposure to dogs with ehrlichiosis	2	nd	nd	*E. chaffeensis*[4]	serology	2 samples 128 titer for *E. chaffeensis* and *A. phagocytophilum*	12643221
Mexico	1999	1	fever, rash	1	nd	nd	*E. chaffeensis*[1]	serology	*E. chaffeensis* titer 128; blood smear negative	10341193
Peru	2009	160	healthy subjects	21	nd	nd	*E. chaffeensis*[2]	serology		19190221
Venezuela	1996	49	43 healthy adults; 6 children with clinical signs	2	1	2	VHE/*E. canis*[1]	culture	isolate from asymptomatic person with 2,560 VHE titer and 320 *E. chaffeensis* titer; 2nd person with titers VHE 640, *E. chaffeensis* 2560 and *E. canis* 1280	8862572
Venezuela	1996	1	"viral" illness	1	nd	nd	*E. chaffeensis*[1]	serology	blood smear; platelet inclusions; 128 *E. chaffeensis* titer	8920030
Venezuela	2008	1	fever; ? Dengue	1	nd	nd	*E. chaffeensis*[1]	PCR	*E. chaffeensis* DNA in blood by nested PCR, blood smear +, 256 *E. chaffeensis* titer with seroconversion; dengue virus seroconversion	18325283
Venezuela	2010	6	fever	nd	1	nd	VHE/*E. canis*[1]	PCR	all VHE PCR+; 5/6 *E. canis* seronegative	17114689
TOTAL		**1550**		**100**	**2**	**2**				

[1, 2, 3, 4] *A. phagocytophilum* serology was not tested ([1]), negative in all tested ([2]), negative in 5 tested ([3]), or positive at 128 titer in all ([4])
VHE = Venezuelan human *Ehrlichia*
Dx = diagnosis
PMID = PubMed identification number
nd = not done

as an infectious agent of dogs, horses, cattle, and wildlife in South America, human infection by this bacterium has not yet been reported either there or in Central America. In a search of PubMed using the phrases "ehrlichiosis", "anaplasmosis", "chaffeensis", "phagocytophilum", and country names in Central and South America, a total of 100 individuals had antibodies reactive with *E. chaffeensis, E. canis* and/or Venezuelan human *Ehrlichia* strain (VHE) of *E. canis* antigens in serologic tests

(Table 1). In addition, 3 symptomatic persons (2 from Venezuela and 1 from Mexico) had blood smear, seroconversion, or PCR evidence of infection by *E. chaffeensis*,[9,12,13] 4 Brazilian patients had clear *E. chaffeensis* seroconversions,[14] while 6 symptomatic patients had PCR evidence of *E. canis* infection (although 5 were seronegative),[8] and 1 asymptomatic seropositive individual was the source of a blood isolate similar to *E. canis*, the Venezuelan Human Ehrlichia (VHE) agent.[7] At least serologic evidence of infection has been detected in Argentina (1 case),[15] Brazil (57 cases),[14,16,17] Chile (2 cases),[18] Mexico (1),[13] Peru (21 cases),[19] and Venezuela (11 cases)[7-9,12] so far.

The median age of those diagnosed with HME and HGA is 47 to 52 years,[11] and for EMLA infection, 60 years,[3] yet all infection has been reported in all age groups.[11] Men are affected more often than women by a ratio of 1.4:1. Infection is often reported in those with HIV infection, where the course can be fulminant.[20] Other immune compromising conditions such as cancer, diabetes, arthritis, or organ transplantation are reported in up to 12% of HME patients.[11] For HGA, increased incidence or severity of infection with HIV infection has not been well documented, and fewer (6.5%) of patients reported pre-existing immune compromising conditions, including asplenia.[11]

The clinical features of infection have been best delineated in patients from the US. Both are generally characterized as undifferentiated fever, and many have a recent history of tick exposure or tick bite within 10 days.[21,22] Patients often present with sudden fever (92-100%), headache (62-93%), myalgia (63-90%), malaise (73-98%), and nausea or vomiting (35-59%). Rash is more frequent in HME (median 26%) than in HGA (median 6%) where coinfection with *Borrelia burgdorferi* and the occurrence of erythema migrans can confound the presentation. Confusion or changes in mental status are reported in 19-22% of HME patients and in 16-17% of HGA patients. The laboratory features especially include thrombocytopenia (61-91%) and leukopenia (44-73%). Increased serum activities of alanine and aspartate aminotransferases, reflective of mild to moderate hepatic lobular inflammation, are frequent in both HME and HGA (69-100%). Both *E. ewingii* and EMLA infection present similarly, but with less morbidity and no deaths have yet been reported.[2,3] The average age is lower and severity of infection worse for a small group of Brazilian patients with HME.[14]

Nearly 50% of HME and 36% of HGA patients require hospitalization.[11] Complications of infection can occur, including a septic- or toxic-shock syndrome, acute respiratory distress syndrome, acute abdominal syndromes, cardiac failure, renal failure, cranial nerve palsies, brachial plexopathy, demyelinating polyneuropathy, meningoencephalitis (for HME), and opportunistic infections.[23] There is very limited evidence that even with recovery from active infection, patients with HGA do not report feeling entirely well up to one year later.[24]

Diagnosis is suspected with undifferentiated fever or an influenza-like illness after exposures to ticks or reported tick-bites, especially given thrombocytopenia with leukopenia and mild to moderate increases in serum AST or ALT. The diagnosis can be confirmed rapidly by review of a peripheral blood or buffy coat smear stained by Giemsa, Wright or similar Romanowsky methods that demonstrate inclusions (morulae) in monocytes in up to 10% of HME patients, or in neutrophils in up to 75% of HGA patients.[25] A specific diagnosis can be made by identification of *Ehrlichia* spp. or *Anaplasma* DNA in blood, CSF or tissues using methods such as PCR. The most frequent method for diagnosis is the demonstration of a seroconversion or four-fold increase in specific antibody titer, which is highly sensitive when comparing acute and convalescent sera, but has not been rigorously tested for specificity. Diagnostic serological tests usually use indirect immunofluorescent methods, where the sensitivity and specificity are highest for IgG antibodies. A role for IgM testing has not been clearly established.

All forms of ehrlichiosis and anaplasmosis appear to respond to tetracycline antibiotics, especially doxycycline, although no randomized clinical trials have been conducted. All isolates so far tested are susceptible to these drugs in vitro at easily achieved MICs.[26-29] Chloramphenicol should not be used owing to lack of in vitro susceptibility and frequent empirical clinical failures. Although *A. phagocytophilum* is sensitive to fluoroquinolones *in vitro*, treatment failures with levofloxacin that required subsequent retreatment with doxycycline are reported.[30] Rifampin has low MICs in vitro and has been successfully used in children in empiric studies.[31,32]

Other forms of human infections by Anaplasmataceae species are reported outside of the Americas, but present potential risks to people and animals residing in the western hemisphere. This includes *Neoehrlichia mikurensis* infection of humans that is reported as ranging from mild febrile illness to a sepsis-like severe infection.[33-36] It is transmitted by *Ixodes ricinus* ticks in Europe and perhaps by *Haemaphysalis ticks* in China, and a related species, *Neoehrlichia lotoris* has been readily found in wild animals in North America.[37] Likewise, *Neorickettsia* spp. related to the human pathogen, *Neorickettsia sennetsu*,[38] are abundantly present in aquatic environments throughout North and South America.[39] Unlike other Anaplasmataceae prokaryotes, *Neorickettsia* are largely vectored by trematodes that require part of their life cycle to pass through fresh water snail species. The greatest risk to humans so far seems to relate to the consumption of uncooked or raw fish products, although no sushi or sashimi-related outbreaks have been reported.

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