# Doxycycline Deficiency Syndrome: Ehrlichiosis

**Paul-Erik Uggeldahl**
*Suvikatu 8, FIN-80200 Joensuu, Finland. E-mail: pe.uggeldahl@gmail.com*

The title of this article highlights the unique role of the antibiotic doxycycline in the treatment of ehrlichiosis. This odd headline was presented in The New England Journal of Medicine, in a report but without mentioning the disease in the title. Later, an important article on human ehrlichiosis was published in Läkartidningen (1). In 2001, the Swedish veterinarian Anneli Björsdorff published her doctoral thesis on Ehrlichia in animals and humans. The author sent me her publication, responding with delight to my interest from a country (Finland) that published many high-class articles on ehrlichiosis, by the veterinarian Jaakko Tuomi, in the 1960s.

Ehrlichiosis is mainly a disease of of domestic animals; cattle, horses, lambs and dogs (1).

In 2003, I presented a paper on the disease, at the spring meeting of The Finnish Dermatological Society in St Petersburg, focussing on human granulocytic anaplasmosis (HGA). After 1999 this topic disappeared from Läkartidningen, which is active in reporting zoonoses and their vectors; ticks and mosquitoes. Much later (in autumn 2013), when preparing a review article for SKINFO, a journal of the Finnish Society of Dermatology, I contacted Anneli Björsdorff, who informed me that the promising research work on Ehrlichia, established in Kalmar, Sweden, had been halted due to lack of funding. My questions concerning progress in diagnostics and the number of human cases thus remained unanswered.

Ehrlichiosis is named in honour of Paul Ehrlich, a German bacteriologist and immunologist. Ehrlichioses are caused by rickettsial bacteria, and the vectors are hard ticks or sometimes soft ticks. There are 5 types of human ehrlichiosis, 2 of which are of clinical importance: human monocytic ehrlichiosis (HME), caused by Ehrlichia chafffeensis, and human granulocytic anaplasmosis (HGA), caused by Anaplasma phagocytophilum. Both of these types exist in the USA, but only HGA is found in Europe. Ehrlichiosis in Europe is transmitted by *Ixodes ricinus*, the hard tick familiar to us from Borrelia and tick-borne encephalitis (TBE).

A new classification of ricketsias was made in 2001, as described in a review article (2). Ehrlichioses are notifiable diseases in the USA, but not in Europe.

*Human granulocytic anaplasmosis*

HGA is caused by a Gram-negative bacteria, borne by a tick vector, which can infect humans after 4–24 h of attachment (blood-sucking). The incubation time for both HGA and HME is 4–21 days (5, 6). The microbe penetrates the white blood cells; granulocytes in HGA, and monocytes in HME, where it multiplies intracellularly. HME does not exist in Europe because the vector, a soft tick (*Amblyomma americanum*) lives only in the southeast of the USA.

*Ixodes ricinus and Anaplasma phagocytophilum: the vector and the microbe*

This bacteria has many reservoirs (animals with living Anaplasmas in their blood), and it is notable that, in addition to small rodents, many large wild animals are reservoirs, especially the deer family are named as reservoirs (the thesis by Björsdorff). On the other side, there are lots of mammals without this living microbe in their bloodstream, and which can, in contrast to reservoir hosts, get sick in ehrlichiosis. Especially the domestic mammals named earlier. Also we, humans. This "group" is named reproduction hosts. It might be expected that the ticks (*Ixodes ricinus* in the Europe, and *I. scapularis* and *I. pacificus* in the USA) would be highly infected with Anaplasma since there are a multitude of reservoirs; however, this appears not to be the case.

Has this topic been sufficiently investigated by medical entomologists? In tick-endemic areas humans have high levels of HGA antibodies, which are present in up to 20% of the population (e.g. in Sweden, and in New England, northeast USA).

## Symptoms

In veterinary medicine granulocytic anaplasmosis is named "pasture fever". A sudden high fever when ticks are active (spring, summer, and autumn), headache (especially in HME), malaise, myalgia could be caused by Ehrlichia (HGA). These are common symptoms in many (infectious) diseases, resembling first and foremost a heavy, prolonged flu, but in the "wrong" season. The protozoan disease babesiosis may also appear with similar symptoms. Sometimes the feeling is as having been beaten and mangled ("as run over by a truck").

Approximately 10% of patients develop a rash, which should be examined by a dermatologist. Two such examples are given in this article (Figs 1–2). In one article the rash appeared on the trunk and upper extremities as an erythema. Skin symptoms are more frequent in HME, especially in children, existing in 30% of the patients. The critically ill patient mentioned in treatment (HME) had a morbilliform rash (3).

In most patients the symptoms disappear after 30 days, even without antibiotic therapy (5). The clinical manifestations and laboratory findings are similar in Europe and the USA, but in Europe the disease appears to be milder and improves more rapidly than in the USA (5). Almost 50% of patients with severe HGA need hospital care, 17% on the intensive care unit (5).

During the acute phase most patients develop thrombocytopaenia and leucopaenia (neutropaenia and/or lymphopaenia) and elevation of hepatic transaminase levels. Also hyponatremia appear which should be typical of ehrlichioses (3). These findings can be observed over a period of 2 weeks, after which they become normal again. Thus, a normal routine blood test does not exclude HGA.

Leucopaenia and thrombocytopaenia may be caused by an inflammatory mechanism triggered by the Anaplasma. Bacterial lysis of the infected cells is not a possible cause, since only a fraction of granulocytes are infected and the thrombocytes are not infected (3, 4).

## Diagnosis

*Serodiagnosis*

The most reliable serodiagnosis is a four-fold increase in immunoglobulin IgM and IgG antibodies, detected using the indirect fluorescent antibody (IFA) method. A blood sample is taken in the acute phase and another approximately one month into the recovery phase (7). A study verified 10 of 12 patients via a polymerase chain reaction (PCR) (1). Bacterial culture is also possible, but is time consuming and expensive.

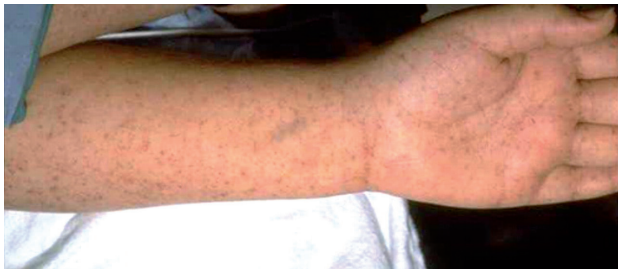

*Fig. 1.* Petechial rash in a patient with human granulocytic anaplasmosis (HGA). ©Richard Jakobs, MD.

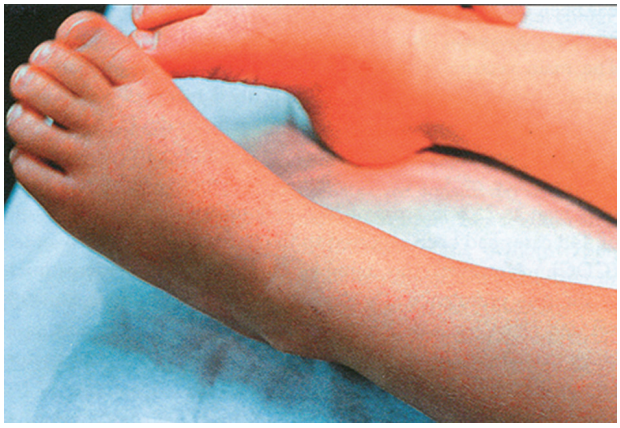

*Fig. 2.* Petechial rash in a child with human granulocytic anaplasmosis (HGA). ©Edwin Masters, MD.

The fastest current method of diagnosis is to examine a Wright- or Giemsa-stained blood smear (Fig. 3). Neutrophilic granulocytes contain so-called morules; clusters of bacteria that reproduce intracellularly. This investigation must be carried out within one week of the start of the infection. In the USA rapid diagnosis of HGA using this technique has succeeded in two-thirds of patients, but, for some reason, has not succeeded in Scandinavia (1). A rapid, sensitive and specific diagnosis does not yet exist.

## Treatment

Doxycycline is the recommended and almost "the one and only" treatment. There must be a clear response to this treatment within 24–48 h. If not, the diagnosis must be re-evaluated (4). A male patient who was seriously ill in HME recovered in hours after 100 mg doxycycline. One pill! His treatment continued with 100 mg daily during 10 days (3).

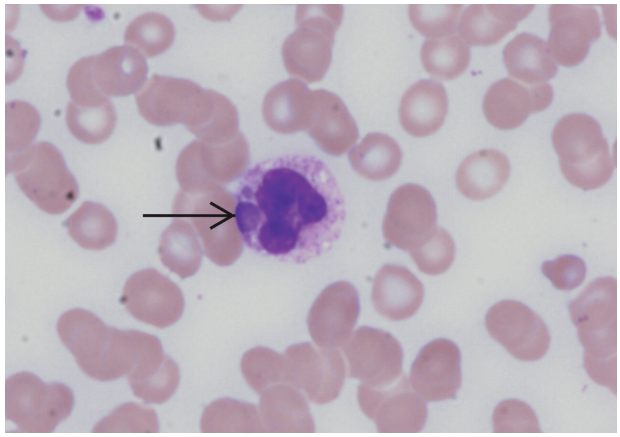

*Fig. 3.* Blood smear stained with Giemsa (cow's blood). An accumulation of Anaplasma phagocyticum bacteria is visible inside a neutrophilic granulocyte. ©Centers for Disease Control and Prevention.

*Recommendation:* Doxycycline 200 mg × 1 × 14 days (1), 100 mg × 1 × 10 days (3) or 100 mg × 2 for 7–14 days (4–6). My choice of doxycycline dosage is 100 mg × 2 × 10 days.

With doxycycline treatment no relapses have been observed (4) and the disease has not become chronic (4–6). For pregnant women, and children under the age of 8 years, the recommended treatment is rifampicin, but in cases of serious disease all patients should be treated with doxycycline. Re-infections do not occur as long as the patient has antibodies in the blood (a period of approximately 1–3 years) (4).

HGA and HME can start very quickly, and these diseases (especially HME) can be fatal. Antibiotic treatment must therefore be commenced immediately when there is a suspicion of either disease, based on the symptoms and a blood test including haemoglobin, red and white blood cells and thrombocytes, and before a confirmatory serodiagnosis is available (3, 5). In cases of serious illness where there is difficulty obtaining a blood test treatment must be started immediately without such results. Of course the anamnesis is of importance, and tropical infectious diseases that may have similar symptoms, e.g. dengue, should also be considered.

## Does HGA exist in Finland?

On 13 December 2002, Anneli Bjöersdorff stated in a letter to me: "I think that human ehrlichiosis also appears in Finland. We consider that the infection is often mild in Sweden, and may even not be noticed. However, we have described many serious cases requiring intensive care, including a respirator."

"In serious events the situation can be complicated by both respiratory failure and influence on the central nervous system. As a further complication opportunistic infections have been reported, in some case with lethal outcome." (1).

Is this a new human zoonosis in Nordic countries? Or, is it a disease that has been hidden until recently? The authors consider this (1).

Although the immunological mechanism behind a serious and fatal HGA is not fully understood, there are indications that immunosuppression occurs in these patients (1, 6).

## Epilogue

My review article on ehrlichioses was published in Finnish in SKINFO in May 2014 (SKINFO 2/2014). The title and introduction have been altered here, but also revisions and additions in the text have been made. Especially the chapter "Symptoms" is more comprehensive.

In November 2014, SKINFO (4/2014) also published my review of babesiosis; "malaria caused by ticks", in which I assumed that some human babesioses and tens of anaplasmoses (HGA) with clinical symptoms appear annually in Finland.

I have not read the latest international reports (since spring 2014) on ehrlichioses; if this paper has aroused your interest, please read further in the literature.

## References

1. Björsdorff A, Berglund J, Kristiansen BE, Söderström C, Eliasson I. Varying clinical picture and course of human granulocytic ehrlichiosis. Twelve Scandinavian cases of the new tick-borne zoonosis are presented. Läkartidningen 1999; 96: 4200–4204.
2. Dumler JS, Walker DH. Tick-borne ehrlichioses. Lancet Infect Dis 2001; 1 (Suppl 1): 1–28.
3. Stone JH, Dierberg K, Aram G, Dumler JS. Human monocytic ehrlichiosis. JAMA 2004; 292: 2263–2270.
4. Bakken JS, Dumler S, Human granulocytic anaplasmosis. Infect Dis Clin North Am 2008; 22: 433–448.
5. Thomas RJ, Dumler JS, Carlyon JA. Current management of human granulocytic anaplasmosis, human monocytic ehrlichiosis and Ehrlichia ewingii ehrlichiosis. Expert Rev Anti Infect Ther 2009; 7: 709–722.
6. Ismail N, Bloch KC, McBride JW. Human ehrlichiosis and anaplasmosis. Clin Lab Med 2010; 30: 262–292.
7. Seppänen M, Vapalahti O. Anaplasma, ehrlichiat and neoriketsiat. Mikrobiologia, Duodecim 2010, p. 279–283 (in Finnish).