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REVISITING ANTHROPOZOONOSES IN THE MEDITERRANEAN BASIN. A SINGLE-CENTRE PERSPECTIVE. A SOUTHERN ITALIAN EXPERIENCE

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Abstract

Zoonoses, often better defined with the term anthropozoonoses, are diseases that can be transmitted to humans either by direct contact with animals or through arthropod vector intervention. Microbial interaction between humans and animals constitutes an important public health challenge, particularly in the Mediterranean basin. The main reasons this challenge is still relevant today include the phenomenon of migration, of both humans and animals, and climate change, which tend to alter the geographical distribution of zoonosis or the zoonotic agent, as well as the distribution range of potential vectors. The Mediterranean area seems to be affected by plentiful and widely distributed zoonoses, the main diseases being rickettsiosis, leishmaniasis, brucellosis, hydatid disease and viral zoonoses. The aim of this study is to revisit the prevalence and main clinical features of anthropozoonoses observed at the Department of Sciences for Health Promotion and Mother & Child Care, University of Palermo, Sicily, Southern Italy.

Keywords: Anthropozoonoses, Mediterranean basin, Sicily

Introduction

The Mediterranean area seems to be affected by plentiful and widely distributed zoonoses. The reasons for this concentration are to be referred to the great biodiversity and the close co-existence between people and animals [1-3]. Zoonoses, an all encompassing term, better often defined with the term "anthropozoonoses" (diseases transmitted to man from other vertebrates), defines a large group of infectious diseases that still represent a public health challenge due to the complex microbial interaction between humans and animals [4-13]. Many zoonotic diseases have disappeared or been eradicated: historical examples are the plague (absent for more than three centuries), canine rabies (or urban, last reported case in 1974), sylvatic rabies and American myiasis (*Cochliomyia hominivorax*, the killer fly, introduced in the 1990s and promptly eradicated thanks to the release into the environment of sterile males). Other zoonotic diseases are still present in the Mediterranean basin: rickettsiosis, leishmaniasis and brucellosis are well-known diseases, while others are emerging and rare [1-3,14-19].

Furthermore, the multidimensional phenomenon of migration, climate change and the increase in national and international transport are changing the geographical distribution of the zoonosis or the zoonotic agent, as well as the distribution range of potential vectors [20-24].

Rickettsiosis

Rickettsiosis is a globally widespread zoonosis caused by gram-negative bacteria belonging to the genus *Rickettsia* and *Orientia*, which are transmitted by arthropod vectors (lice, fleas, ticks and mites). In Europe only the species belonging to the genus *Rickettsia* are responsible for Rickettsiosis, and typically fall into two general groups: the spotted fever group and the typhus group.

The endemic typhus (murine typhus) caused by *Rickettsia typhi* and transmitted by the rat flea (*X. cheopis*) is common in Mediterranean countries (Spain, Croatia, Greece, Cyprus). *Rickettsia felis* is found in the cat flea (*C. felis*) with high vector prevalence in Europe [25].

However in Europe the predominant rickettsioses belong to the spotted fever group.

Mediterranean spotted fever (MSF), one of the oldest-recognized vector-borne infectious diseases, is an endemic zoonosis in the Mediterranean basin. MSF is caused by *Rickettsia conorii subsp. conorii* and it is endemic in southern Europe with sporadic documented cases in some regions of northern and central Europe; *Rhipicephalus sanguineus* is the principal vector and reservoir. The clinical presentation includes fever, maculopapular rash, and the presence of a tache noir on the tick bite site. Most of the time the clinical course is positive, with a mortality rate of 3-7% in hospitalized patients. Most cases are reported in the summer months, when ticks are very active. In the southern European region the higher temperatures permit the persistence and abundance of ticks and for this reason cases can be reported during the spring. In Italy, each year about 300 MSF cases are reported, of which more than half are in Sicily [26,27]. *Rickettsia conorii subsp. conorii* has long been considered the only pathogen rickettsia in Europe. However, in recent decades the use of molecular biology techniques allowed the identification of new rickettsia species and subspecies as new emerging pathogens responsible for new clinical diseases different from the classical form of FBM: *Rickettsia conorii subsp. israelensis, Rickettsia conorii subsp. caspia, Rickettsia conorii subsp. indica, Rickettsia slovaca, Rickettsia raoultii, Rickettsia monacensis, Rickettsia massiliae, Rickettsia aeschlimannii, Rickettsia helvetica, Rickettsia sibirica subsp.sibirica and Rickettsia sibirica subsp mongolitimonae*. In 1996 and 1997 in France the first case of human infection with *Rickettsia slovaca* and *Rickettsia sibirica mongolitimonae* was described; *Rickettsia massiliae* was identified for the first time in Marseille and was recognized as a disease agent in Sicily in 2006 [28]. In 2003 in Sicily, *Rickettsia conorii* subsp.*israelensis* was identified, agent of the Israeli spotted fever (ISF), documented in Italy (Sicily and Sardinia) and in other Mediterranean

areas (e.g. Portugal). The distribution of ISF has proved to be wider than previously thought, and it is now possible to assert that many of the MSF severe clinical pictures described in the literature should be attributed to R. rickettsii subsp. Israelensis [29]. Lastly, TIBOLA / DEBONEL / SENLAT, acronyms for respectively, 'Tick-Borne Lymphadenopathy' / 'Dermacentor-Borne Necrosis Erythema Lymphadenopathy' / 'Scalp ESCHAR and Neck Lymphadenopathy After Tick Bite', are caused by *Rickettsia slovaca*, *Candidatus Rickettsia* and *Rickettsia raoultii*. The main vector in these cases is *Dermacentor marginatus* and the major symptoms are necrotic eschar on the scalp associated with painful cervical lymphadenopathy [28].

Although MSF is mostly a self-limited disease characterized by fever, skin rash, and a dark eschar at the site of the tick bite called a 'tache noire', serious complications have been described, mainly in adult patients [30-35].

Tetracyclines are considered standard treatment for MSF, even though they can cause significant adverse effects like staining of the teeth and bone toxicity, especially in children. For this reason, macrolides have emerged as a potential alternative therapy in children [36-38].

Leishmaniasis

Leishmaniases are a group of vector-borne parasitic diseases caused by protozoa belonging to the genus Leishmania. Generally, Leishmania infection is transmitted to humans and to other mammals by the bite of an infected sand fly vector. Rarely, the infection can be transmitted through blood transfusions, by needle sharing, or from mother to child during pregnancy. The World Health Organization (WHO) has stated that leishmaniasis is one of the most neglected diseases, with 350 million people considered at risk of contracting the disease, a burden of about 12 million people currently infected in 98 countries, and two million new cases estimated to occur annually. Among these, visceral leishmaniasis (VL) accounts for about 500 000 cases each year. The clinical spectrum includes cutaneous, mucocutaneous and visceral forms. Asymptomatic infections have also been demonstrated, but their role has yet to be clarified.

Parasite, vector and host, and their complex interplay, determine the different clinical forms of VL [40]. It has been estimated that in endemic areas the proportion of asymptomatic infections is 5–10 times greater than the number of clinically apparent VL cases in immunocompetent hosts. Cryptic infection can be detected in people without a previous history of clinical VL by serological evidence of anti-Leishmania antibodies, by detection of parasite DNA in blood samples, or by a positive reaction to the leishmanin skin test (LST) [41,42]. Asymptomatic infection has also been demonstrated in HIV-infected patients. Also in this population, the percentage of asymptomatic infection could be higher than symptomatic cases. Leishmania parasitemia was found to be significantly higher in patients with higher viral loads. A high parasitemic burden could possibly be related to a higher risk of developing symptomatic disease, due to the reciprocal effects that enhance the multiplication of both pathogens [42-44].

In the immunocompetent host, VL is caused by a primary infection with Leishmania parasites transmitted by the bite of a phlebotomine sand fly. VL is the result of a chronic infection; the incubation period ranges from 10 days to 1 year. Clinical features of typical forms are fever, weight loss, hepatosplenomegaly, and pancytopenia. Fever can be intermittent in the first period and successively continuous. Non-tender splenomegaly and hepatomegaly are caused by infection of the reticuloendothelial system. Pancytopenia caused by parasites invading the bone marrow is responsible for pallor due to anaemia, and can subsequently cause haemorrhages due to thrombocytopenia and concurrent infections due to leukopenia. Anorexia and weight loss can lead to wasting syndrome in misdiagnosed cases [44-47]. PCR on peripheral blood allows a rapid and non-invasive parasitologic diagnosis of VL [48,49].

Leishmaniasis has been reported among transplant recipients, HIV patients and among other immunosuppressed patients [41,50,51].

Anti-leishmanial treatment is based on the systemic administration of one or a combination of effective drugs. Alongside pentavalent antimonials, which have been the standard first-line medicines for many decades, new anti-leishmanial drugs such as lipid formulations of amphotericin B, miltefosine, and paromomycin are currently used for the treatment of VL. Lipid formulations of amphotericin B, and in particular liposomal amphotericin B, are considered to be the drugs of choice for the treatment of VL [52,53].

Case reports and small series have anecdotally reported the successful use of liposomal amphotericin B or pentavalent antimony in VL complicated by secondary hemophagocytic lymphohistiocytosis [49].

Conditions of depression of the immune system, such as HIV infection or immunosuppressive treatments in transplant recipients and in patients with autoimmune diseases impair the capability of the immune response to resolve the infection and allow the reactivation of the disease from sites of latency of the parasite. Reactivation of chronic infection can occur long after primary contact with the parasite [52-55]. Appropriate screening for leishmaniasis before beginning immunosuppressive treatments could be useful for calling to attention the potential risk for VL in the immunocompromised host. The LST (Montenegro test), an intradermal injection of a suspension of killed promastigotes, measures delayed hypersensitivity reactions and appears to be valuable for detecting asymptomatic Leishmania infections [56].

Brucellosis

Brucellosis is a zoonotic infection in domestic and wild animals that is caused by organisms of the Brucella genus. Humans become infected by ingesting unpasteurized dairy products, being in direct contact with infected animals, or inhaling infectious aerosols. Brucellosis is one of the world's most widespread zoonoses. The distribution of this disease is worldwide, and areas of high endemicity include the Mediterranean, the Middle East, Latin America and Asia [7,57]. Domestic animals harbouring *Brucella* spp. are raised where adequate control measures are lacking and where the population has the custom of ingesting unpasteurized milk or its products. In Sicily, the largest Italian island, brucellosis is highly endemic and has shown a marked resurgence in the last few years (14 cases per 100,000).

However, fewer than 200 cases are reported per year (0.04 cases per 100,000 population) in the United States.

Brucella spp. are intracellular pathogens that can survive and multiply within mononuclear phagocytes (monocytes and macrophages) of the reticuloendothelial system (RES). Localization within organs of RES may explain some of the clinical manifestations of systemic brucellosis, such as hepatosplenomegaly and the propensity for involvement of the skeletal system. Lack of feasible microbiological methodologies [58] or effective treatment may result in serious and sometimes life-threatening complications such as spondylitis, endocarditis and encephalitis [59-62].

Patients frequently experience relapse, even with treatment, and the disease often becomes chronic (i.e., a clinical manifestation of >6 months duration).

Tolomeo et al. have shown that a high level of apoptosis resistance among monocytes and lymphocytes during and after therapy may therefore represent an index of chronic illness, suggesting to the clinician, in some cases, that a change in therapy is required [63].

The treatment of choice for acute brucellosis is considered a 6-week regimen of tetracycline administered orally in combination with streptomycin (1 g/day intramuscularly for 2-3 weeks). Although other antibiotics have been used, no substantial improvement in relapse rates has been reported in association with any new treatment regimen in the past 45 years [4]. In 1986, the World Health Organization (WHO) recommended therapy with the combination of doxycycline (200 mg/day) plus rifampin (600-900 mg/day) both administered once daily by mouth for 6 weeks [64,65].

Cascio et al. [63] showed that the combination of intravenous rifampin plus oral minocycline administered for 3 weeks obtained the lowest relapse rate (1.7%). This combination therapy, like those reported by WHO (i.e. doxycycline plus rifampin) versus streptomycin plus doxycycline, showed a relapse rate of 16% and 5.3%, respectively [66].

Experience with different treatments in childhood brucellosis is sparse and generally tetracyclines are not used in children ≤8 years of age [67,68]. Cascio et al. have published a study suggesting that minocycline could be used (for a maximum of 3 weeks) to treat infections in pediatric patients when indicated [69].

Other rare zoonotic diseases

Erysipelothrix rhusiopathiae is a common commensal or pathogen of many vertebrate and invertebrate species. Pigs are a major reservoir. Human disease is mainly an occupationally acquired zoonosis. The portal of entry is typically a puncture wound or abrasion on the hand; however, it can also be acquired from eating contaminated food [70].

The global burden of leptospirosis remains enormous and new aspects of the disease are constantly being recognized [71].

Of note, animal rotaviruses, astrovirus, and picobirnavirus might be able to cross species barriers, and lack of systematic surveillance of rotavirus infection in small animals hinders the ability to establish firm epidemiological connections [14,71-75].

Echinococcosis and other helminthic diseases are endemic in Southern Italy [8,9,18].

Over the last ten years, studies have confirmed that besides mammals, birds too are responsible for arthropod human infestation. Migratory wild birds play an important role in the ecology and circulation of potential zoonotic pathogens in Sicily [76,77].

Castelli et al. showed how the bite of an avian arthropod, such as Ornithonyssus species of bird parasite, could be responsible for dermatitis in a Sicilian patient [77].

In conclusion, Southern Italy and Sicily in particular could be affected by emerging diseases caused by the passage of animals carrying arthropods other than well-known ones such as ticks, and this might be the consequence of climate tropicalization, which carries unpredictable epidemiological and ecological implications.

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