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Rocky Mountain Spotted Fever

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Received: Sept 28, 2022 Accepted: Dec 1, 2022

INTRODUCTION

Rickettsia (R), is a small obligatory, intracellular gram-negative bacterium that infect both humans and animals (Dunning Hotopp et al. 2006). In 1909, Howard Ricketts was the first person to discover the genus Rickettsia (Ricketts 1909). On the basis of serological features, it has been classically classified into three distinct groups including the typhus group (TG), spotted fever group (SFG), and the scrub typhus group (STG). Both TG and SFG are under the genus Rickettsia and the STG is under the genus Orienia (Tamura et al. 1995; Dumler et al. 2001; Bermúdez 2018). There are only two species of TG rickettsiae: *R. prowazekii*, which is transmitted by louse; and causes a disease named epidemic typhus, and *R. typhi*, which is transmitted by flea and causes a disease named murine typhus. While there are more than twenty species of SFG and all species are transmitted by hard ticks except two species including *R. akari*, being transmitted by mites, and *R. felis* being transmitted by flea (Greene and Breitschwerdt 1998; Foil and Gorham 2000; Centers for Disease Control and Prevention, National Center for Infectious Diseases 2002). *R. rickettsii*, is the causative agent for Rocky Mountain spotted fever (RMSF) and comes in the group Rickettsia (Williams et al. 2007).

The differential features of TG and SFG group involve the polymerization of actin, type of outer membrane proteins and difference in the optimal growth temperature. The TG group cannot polymerize the actin and enter the host cell cytoplasm, have type B outer proteins and show optimal growth at 35°C while the SFG group can polymerize the actine and enter the host cell nucleus, have type A and B outer proteins and show optimal growth at 32°C (Fournier and Raoult 2007). The last difference is the difference in the ratio of genomic G-C, which is 29% in case of TG, while it is 32% -33% in case of SFG (Gillespie et al. 2007).

Like other bacteria, Rickettsiae have both deoxyribonucleic acid (DNA) and ribonucleic acid (RNA) and they secrete substances, generate energy and perform all other living activities. Rickettsiae are transmitted to the host during biting and the blood meal by the infected ticks. It is transmitted from the site of bite by the bloodstream to infect the endothelium and sometimes to the vascular smooth muscle cells. Rickettsia species in their target cells can multiply by binary fission and cause direct damage to heavily parasitized cells (Walker and Ismeil 2008).

Rocky Mountain Spotted Fever (RMSF)

Many studies approved that the RMSF was found in America before humans arrived there and this is due to the hard tick that transmits the *R. rickettsia* through trans-ovarian way. The hard ticks have acquired the infection from feeding and biting of infected animals and they lay infective eggs and the pathogen was transmitted to the whole generation of tick (Burgdorfer 1963). In North America, human infections with *R. rickettsii* have been recorded, and was named Rocky Mountain spotted fever (RMSF). It is named as fiebre maculosa Brasileira' in Brazil and fiebre de Tobia in Columbia (Oteo et al. 2014). RMSF is an acute fatal bacterial disease that infects humans of different ages and dogs. It is transmitted by the bite of an infected hard tick in two ways: by trans-ovarian and trans-stadial transmission (Walker and Raoult 2000; Savic 2019). The disease is characterized by fever, chills, rash, and muscle aches (Warner and Marsh 2002). RMSF is still considered as the most virulent disease among all human infectious diseases, mainly in young people in North and South America (Warner and Marsh 2002; Bermúdez 2018).

History of RMSF

Firstly, the RMSF was identified as black measles and was reported for the first time in the late 1890s, in Idaho and Rocky Mountain, so it was named Rocky Mountain spotted fever (Ricketts 1909; Azad and Beard 1998; Centers for Disease Control and Prevention website 2017). In 1906 Howard Ricketts discovered that RMSF was a bacterial infection that was transmitted to humans by hard ticks (Thorner et al. 1998). Initially, the disease was localized at Rocky Mountain, and then the disease has been observed throughout different regions of America (Centers for Disease Control and Prevention 2022). The disease spread to various countries such as Colombia, Brazil, Mexico, Costa Rica, Argentina, and Panama (Razzaq and Schutze 2005; Dantas-Torres 2007). Over the past 20 years, the

Citation: Ismael SS, 2023. Rocky mountain spotted fever. In: Aguilar-Marcelino L, Younus M, Khan A, Saeed NM and Abbas RZ (eds), One Health Triad, Unique Scientific Publishers, Faisalabad, Pakistan, Vol. 3, pp: 53-59. https://doi.org/10.47278/book.oht/2023.77

incidence of RMSF has been continuously rising in the United States, reaching a peak in 2012. The mortality rate has been shown elevated in older patients more than sixty years of age, in individuals who have been lately diagnosed, and in those who do not receive doxycycline drug as a treatment (Holman et al. 2001; Biggs et al. 2016).

Synonyms for RMSF

RMSF disease is also known with various names such as tick-borne typhus fever, tick fever, black measles, black fever, Mexican spotted fever, and New World spotted fever (Harwood and James 1979).

Vector for RMSF

The common vectors for the transmission of RMSF are hard ticks, mainly *Dermacentor* (*D.*) *andersoni* (Rocky Mountain wood) and *D. variabilis* (American dog tick) (Levin et al. 2017; Ismael and Omer 2021). These two species of ticks are considered as the common species in the northwestern states and the eastern United States. Ticks need several factors to complete their life cycle for the hatching of eggs and molting which include a suitable host, suitable humidity, oxygen, appropriate temperature, and a proper place (Estrada-Peña et al. 2012). Various species of hard tick act as the vector for RMSF and this depends on the geographical area for example; there are three common species of hard ticks in North America including *Rhipicephalus* (*R.*) *sanguineus* (brown dog tick), *D. variabilis* (American dog tick) (Fig. 1) and *D. andersoni* (Rocky Mountain wood tick) (Fig. 2). Both *Amblyomma* and *Rhipicephalus* act as the main vectors for RMSF in Central and South America, mainly in Costa Rica (Oteo et al. 2014; Levin et al. 2017; Ismael and Omer 2021). Additionally, several species of hard ticks have been reported in America such as *Amblyomma imitator, Amblyomma parvum, Amblyomma americanum, Haemaphysalis leporispalutris,* and *Dermacentor nitens* (Labruna and Mattar 2011).

A hard tick has a complex and long-life cycle; involving four morphological stages during their life cycle including the egg, larva, nymph, and adult (Fig. 4). The adult female lays eggs, which is then converted in to larvae. The process of converting each stage is called molting. Hard ticks remain on the host for a short period or during their whole life cycle. During this time, they consume various numbers of blood meals during biting (Walker and Raoult 2000; Golezardy 2006; Williams et al. 2007). The hard tick's life cycle begins once an engorged adult female tick found a proper area to lay her eggs. Normally, the hatching of eggs occurs within one to four weeks. The released larvae are very small in size, light in color and have six legs. Larvae are responsible to find a new animal host for feeding on blood and complete its life cycle (Brumin et al. 2012; Tian et al. 2020).

The host is infected with disease, when the larvae attach to the suitable host and feed on its blood by using its mouthparts (including chelicerae and hypostome), leading to the initiation of infective stage into the host blood (Varela-Stokes et al. 2009). After that, the larvae drop off on the ground and molt to the second stage of the tick called a nymph, which may form one or more nymphal stages and the number of molting differs according to the species of hard ticks and environmental conditions such as temperature and optimal humidity (Walker and Raoult 2000; Tian et al. 2020). The nymph stage then feeds on the host and as usual, they drop off again on the ground and molt to adult males and females. Both nymph and adult stages are brown and have eight legs, and an adult female feed on the host till become engorged. Engorged females lay thousands of eggs on the ground and these depend on the species of hard ticks and environmental conditions (Sen et al. 2012).

The Role of Dogs in RMSF

R. sanguineus (brown dog ticks) infect both humans and animals (Demma et al. 2005; Yaglom et al. 2018). It was identified for the first time during the RMSF outbreak as a potential vector of *R. rickettsii* in North America, and the role of stray dogs has been suggested as reservoirs and primary hosts for the Rhipicephalus at the same time (Demma et al. 2005; Nicholson et al. 2006). In North America, brown dog ticks that transmit the *R. rickettsii* can transmit many other pathogens such as *Anaplasma* spp., *Babesia* spp, *Bartonella* spp., and *Ehrlichia* spp. (Higuchi et al. 1995; Mathew et al. 1996; Wikswo et al. 2007; Diniz et al. 2010). Due to these characteristics, there are increasing outbreaks of RMSF in countries that have a large number of stray dogs (Yaglom et al. 2018).

Pathogenesis of RMSF

The causative agent of RMSF, *R. rickettsii* infects and replicated within the endothelial cells that line the small blood vessels, causes systemic vasculitis and is the main cause of skin rash and petechial lesions on the skin (CDC 2019). The bacteria cause direct injury to microvascular lining and damage to vascular endothelial cells. The endothelial cells release more prostaglandins which may increase the vascular permeability and escape of high amount of fluid into the neighbor tissues resulting in edema and loss of blood volume (Rydkina et al. 2006; Zhou et al. 2022). Injury and damage of blood vessels lead to the inflammation known as vasculitis and this cause bleeding and clotting in vital organs, mainly the brain. Many other pathological changes may occur due to host response to RMSF such as encephalitis, myocarditis, and interstitial pneumonitis (Sahni et al. 2021; Zhou et al. 2022). The severity of the infection and clinical signs depend on several factors including age, sex, body color and history of chronic disease i.e., diabetes mellitus. (Pearce and Grove 1987; Parola et al. 2003).

Fig. 1: Adult tick of *Dermacentor variabilis* (female) (Biggs et al. 2016)

Fig. 2: Adult tick of *Dermacentor andersoni* (Female)(Biggs et al. 2016)

Fig. 3: Adult of *Rhipicephalus sanguineus* (Female) (Biggs et al. 2016)

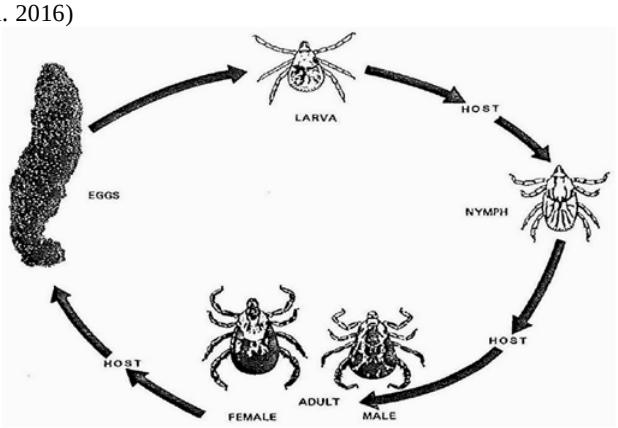

Fig. 4: Life cycle of Hard Tick (Varela-Stokes et al. 2009)

Clinical Symptoms of RMSF

Usually, the incubation period of RMSF ranges from 2 to 14 days following a tick bite. Most tick bites are painless, and some people may not even remember getting bitten, while in Brazil one case was reported with an incubation period ranging between 1-21 days. RMSF is characterized by nonspecific clinical signs such as fever (37 ºC -39ºC), headache, muscle pain, vomiting, and nausea. It may lead to rash, breathing difficulty, abdominal pain, seizure, and shock if not treated correctly (Paddock and Childs 2003; Gottlieb et al. 2018). The typical rash usually appear following 2-4 days of fever and in some cases may appear between 1-6 days. The rash initially appeared as small flat, pink papules on the ankles and wrist and then distributed to the legs, arms, and body trunk (Fig. 5). By the end of the first week, the rash develop into a maculopapular rash with central petechiae (CDC 2000; Regan et al. 2015; Lindblom 2016; Elzein et al. 2020). In RMSF, a skin rash may be not obvious in patients with dark skin (Kirkland et al. 1995; Rathi and Rathi 2010). Children also showed similar signs of RMSF as in adults. A study found a serious case of RMSF in the child sixteen months old, presented with persistent high-grade fever lasting longer than a week and a skin rash that dramatically involves the palms and soles of the feet (Fig. 6 and Fig. 7) (Inamadar and Aparna 2019). The skin rash appears early in children as compared to adults (Purvis and Edwards 2000; Murali et al. 2001). The common symptoms in children include facial swelling, swelling of legs and generalized body edema, enlargement of the liver and spleen, pneumonia, hyperemia, and vasculitis of the eyes (Fig. 8) (Azad and Beard 1998; Chapman et al. 2006; Agahan et al. 2011).

Diagnosis of RMSF

1. Clinical Diagnosis

At the early phase of disease, it is very difficult to differentiate between RMSF and other diseases that have the same clinical signs such as high fever, chills, fatigue, and myalgia. Therefore, its unable to suspect the RMSF at beginning of the disease, because of no specific signs, while in the advanced stage of the disease is easy to differentiate between RMSF and other diseases, because of special petechial skin rash and eschar formation (Paddock and Childs 2003; Gottlieb et al. 2018).

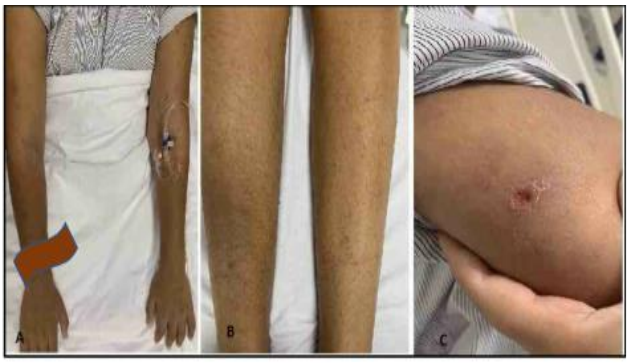

Fig. 5 (A & B): Rash on the upper and lower limbs C. Eschar in the arm (Elzein et al. 2020)

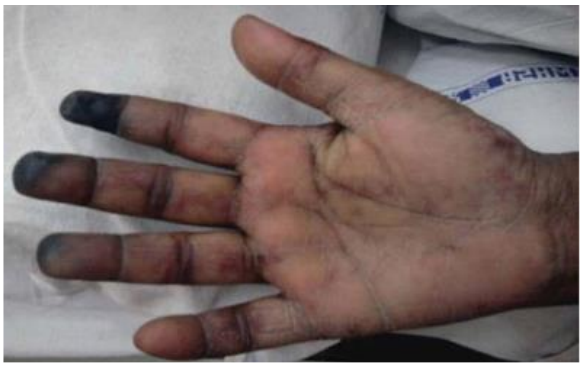

Fig. 6: Sixteen months old child with a clear rash on their palms (Inamadar and Aparna 2019)

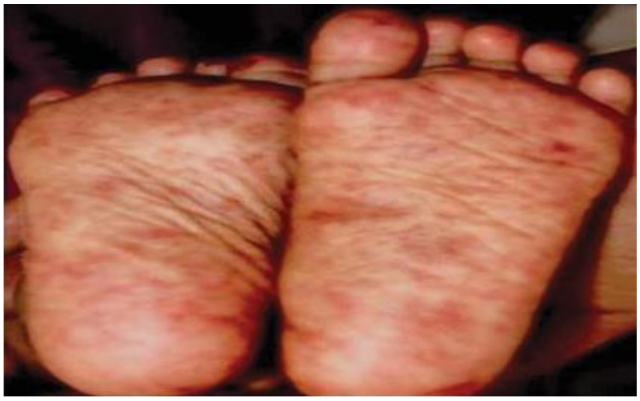

Fig. 7: Sixteen months old child with a clear rash on their foot soles (Inamadar and Aparna 2019)

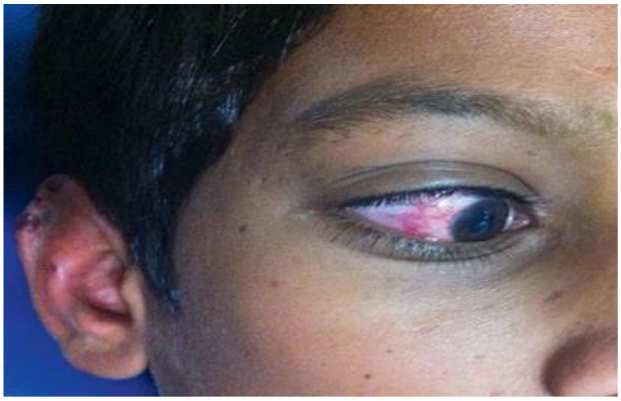

Fig. 8: Hyperemia found in the child's eye (Inamadar and Aparna 2019)

The early diagnosis depends on the history of the disease such as patients having tick bites (specific skin lesion) and previous exposure to the endemic region where for RMFS (Chen and Sexton 2008)

2. Laboratory Diagnosis

Serological test such as indirect immunofluorescence antibody assay (IFA) is considered the main standard test for the diagnosis of rickettsial specie. Antibodies are commonly detected after the onset of infection between 7-10 days. The sensitivity and specificity of IFA are about 94-100% and 80 % respectively and it depends on the time of blood collection (before or after 14 days of infection). The second is enzyme-linked immunosorbent assay (ELISA), which is also used for the detection of antibodies (Ehrlichiosis, 2004; Biggs et al. 2006).

Immunofluorescence staining test, is used to detect both fatal and non-fatal types of RMSF, by taking a biopsy from the skin rash for detection of *R. rickettsii*, and it has been proved by many studies to be sensitive and specific (70%-100%) respectively (Walker 1995; Demma et al. 2005).

Histopathological method, is used for the detection of skin rickettsial antigen. It is done by taking a biopsy from the skin rash, followed by the preparation of a smear and staining with eosin and hematoxylin stain. The infiltration of mononuclear cells which surrounds the vascular system of skin are shown under the microscope (Sexton 2011).

Immunohistochemical staining test, is another test used for the detection of RMSF. The sensitivity and specificity of this test ranges from 70-100 % respectively. It is also used for the detection of skin rickettsial antigen as in histopathological method while under the microscope it appears as focal lesion (Kao et al. 1997; Stewart and Stewart 2021).

The Polymerase Chain Reaction assay (PCR) is highly effective for detection *R. rickettsii* DNA in skin rash biopsy than in blood samples and this is due to *R. rickettsii* being concentrated more in skin rash in advanced stages of disease than in the blood sample (Demma et al. 2005; Institute of Medicine US 2011; McQuiston et al. 2014).

Treatment of RMSF

The recommended drug for the treatment of all types of rickettsiae infection is doxycycline which should be prescribed immediately after RMSF is diagnosed. Doxycycline is highly effective on intracellular bacteria and

its use is safe in children, therefore, doxycycline is recommended as a specific treatment for RMSF by the American academy of pediatrics community. Rickettsiae has resistance to many antibiotics that have lower activity on intracellular bacteria such as cephalosporins, aminoglycosides and trimethoprim-sulfametoxa- zoleand penicillins (Todd et al. 2015; Biggs et al. 2016). Doxycycline is recommended for the effective treatment of RMSF for adults and children (Minniear and Buckingham 2009; Todd et al. 2015; Biggs et al. 2016).

The recommended dosage of doxycycline, for adults, is about 100mg every 12 hours which may be given orally or IV. For children, it is 4mg and should be divided into two dosages and given every 12 hours (orally or IV). Doxycycline should be given for three days as a minimum, while in the severe cases, it should be given at least 5-10 days. In the case, of patients allergic to doxycycline, chloramphenicol is the second drug of choice for RMSF (Thorner et al. 1998; Thomas et al. 2009; Todd et al. 2015).

Prevention and Control

Till now there is no available vaccine for RMSF. Therefore, to decrease the morbidity and mortality of RMSF in endemic regions, it should be diagnosed properly and suspected patients should avoid to visit endemic areas in spring and summer seasons (Helmick et al. 1984; Drexler et al. 2014). Early steps of prevention include the protection from the bite of ticks, reducing contact with tick population, mainly from forested, and grassy regions and finally ticks that are adhered to the body should be removed carefully (Centers for Disease Control and Prevention Tick Removal 2016).

Conclusion

RMSF is a zoonotic tick-borne disease found worldside that infects humans (including adults and children) and dogs and is transmitted by hard ticks. It is considered as one of the main public health issues because of its high prevalence and effects. It is not promptly recognized and diagnosed, and may leads to death. The two factors that leads to death include the delayed or incorrect diagnosis of the case because of no early specific sign and the delayed treatment of cases with doxycycline because if a patient does not receive doxycycline during the first five days may lead to many systemic complications. Finally, the suspected patients who have a history of tick bites, or have fever and skin rash in an endemic region should be treated carefully. Save people's life from RMSF in endemic regions, is depending on the early accurate diagnosis and correct treatment to prevent the occurrence of fatal complications. It is the responsibility of the public health sector to prevent and control the disease in the endemic regions by reducing the tick population and reducing stray dogs because dogs play an important role in the RMSF.

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