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Rickettsial Infection: An Overview of Clinical, Epidemiological, Diagnostic Features. Case Report with Neurological Complication

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Abstract

Rickettsia infection can have a severe course and cause neurological complications. Early diagnosis and precocious treatment may prevent complications, which are often severe and may depend on the patient. We present a case-report of a young child with Rickettsia infection showing neurological complications. We also present a review of the epidemiological, clinical, and diagnostic features of Rickettsia infections. Rickettsia infection and its complications were searched on online databases, such as MEDLINE, Embase, PubMed, Cochrane central, and Scopus. As far as encephalitis-like neurological complications are concerned, the organisms infect vascular endothelial cells, producing inflammatory microvasculitis with endothelial proliferation, which determines perivascular glial nodules pathognomonic for Rickettsia, alters vascular permeability, causing thrombosis, micro-infarction, and hemorrhages, up to coagulation phenomena disseminated intravascular disease (DIC). The diagnosis of the disorder is mainly clinical as serological confirmation may be late, due to the delayed appearance of antibodies against rickettsia. Rickettsia infection may have a severe course. It is worthwhile to know the diffusion of the Rickettsia species and vector in each geographic area, to early recognize the main clinical manifestations of the illness and rapidly request the diagnostic confirmatory diagnostic tests, and to begin as soon as possible the right antibacterial therapy to prevent severe complications.

Keywords: Rickettsia; Pediatric Rickettsiosis; Treatment

Abbreviations: BF: Breast Feeding; UNICEF: United International Children Emergency Fund; WHO: World Health Organization; GCC: Gulf Cooperation Council

Introduction

Rickettsia spp. obligate intracellular Gram-negative bacteria causing infections with various clinical spectrum ranging from a mild febrile disease to several life-threatening conditions. Their life cycle requires both vertebrate hosts and vectors such as ticks, clothing lice, fleas, mites, or others. Humans do not have an essential role in the natural cycle: they participate only when they are stung by a vector insect, representing incidental hosts, except for R. prowazekii. Rickettsioses have a global diffusion and represent an important cause of morbidity and mortality worldwide, despite the availability of effective drug treatment,

especially during epidemic outbreaks [1]. Clinical manifestations are nonspecific, leading to an extensive differential diagnosis and, too often, to a diagnostic delay. In addition, children are among the most affected age groups [2]. Rickettsiosis is a group of diseases caused by different bacteria, such as Orientia, Ehrlichia, Anaplasma, and even Coxiella species, although they take their name from the most known species of the genus Rickettsia. In fact, the order Rickettsiales comprises two families. Anaplasmataceae, in-cluding Anaplasma phagocytophilum, Anaplasma marginale, Ehrlichia chaffeensis, Ehr-lichia ewingii, Neorickettsia sennetsu and Wolbachia, and Rickettsiaceae, which includes Orientia tsutsugamushi and Rickettsia spp. Despite belonging to different families, the diseases caused by these bacteria often have similar clinical features [3,4]. Recent studies, based on whole genome sequencing, have led to a more detailed classification, thus allowing a recent distinction of the genus Rickettsia into four groups: a spotted fever group (SFG), including R. rickettsii, R. conorii among the most important pathogens; a typhus group (TG), including R. prowazekii and R. typhi; an ancestral group, including R. bellii and R. canadensis and the recently formed transitional group, including R. akari, R. aus-tralis, and R. felis [5].

The presence of the gene encoding the outer membrane protein A (OMPA) allowed a clear differentiation among bacteria belonging to SFG and TG. Full genome sequencing further defined the distinction, showing that some species possess the ompA gene, but are genetically different from others belonging to the spotted fever group. A recent review highlighted the small genome size of Rickettsia spp, ranging from 0.8 to 2.5 Mbp, composed by around 420 genes, which code for 88 to 536 different proteins [6]. Many members of the spotted fever group are pathogenic to humans. Classical manifestations include high fever, maculopapular rash, and the tache noire. However, the disease might involve any organ, and, in this case, it is more severe and often complicated. Severe disease is dominated by skin rash and evolves with neurological complications. We present a case-report of a young child with Rickettsia infection showing neurological complications. We also present a review of the epidemiological, clinical, and diagnostic features of Rickettsia infections.

Materials and Methods

The review was conducted by collecting clinical trials, primary research, and reviews from online bibliography databases (MEDLINE, Embase, PubMed, Cochrane Central, and Sco-pus) from January 2015 to October 2022). The key search from the medical subject heading terms were the following: “Rickettsioses”, “Tickborne rickettsials diseases”, “Rickettsioses and neurological complications”, “rickettisioses and treatment”. After removing duplicate records, the main research related to the study was included.

Case Report

A 6-year-old girl previously in good health was admitted to Policlinico-San Marco Hospital Section of Pediatrics and Child Neuropsychiatry in Catania, after 8 days of fever. She had had one episode of generalized tonic-clonic convulsions, retrovulsion of the eyeballs, and altered sensorium, The episode lasted 10 minutes. After three days of fever, she had also shown skin eruption over the face and limbs. On admission, the nasopharyngeal swab for SARS-COV-2 was negative.

Physical examination revealed a temperature of 38.6 °C. A maculopapular rash was found over the face and both hands and feet, involving palms and soles. Edema of hands and lower limbs was present, although there was no lymphadenopathy, conjunctivitis, eschar, or ear discharge. Both liver and spleen were enlarged. No cranial nerve palsy or focal neural deficits were highlighted. There was no evidence of papilledema on fundoscopy. Her parents referred to a possible contact with homeless dogs affected by tick infestation around their residence, but no known history of tick bite. On blood exams, hemoglobin was 8.1 mg/dL, white blood cell (WBC) count was 17,600/μL with 78% neutrophils and 17% lymphocytes. The platelet count was 64.000 mm3. Peripheral blood smear was negative. Blood sugar was 130 mg/dL and serum electrolytes were normal. Serum alanine transaminase (ALT) was 115 IU/L.

A cranial computed tomography (CT) scan turned normal on magnetic resonance (MRI) hyperintense lesions were seen, especially in the temporal region. Examination of CSF sample obtained by lumbar puncture revealed a WBC count of 180 cells/μL with 11% neutrophils and 89% lymphocytes, a glucose level of 65 mg/dL and a protein concentration of 87 mg/dL. Stains and cultures for bacteria, mycobacteria, and fungi were negative. The patient was started on ceftriaxone (80 mg/kg/day in one daily dose) intravenously.

The presence of palmoplantar rash, its distribution, the clinical characteristics, and history, suggested a Rickettsia infection with encephalitis complication, and a treatment with chloramphenicol 50 mg kg/day in four doses and doxycycline, two loading doses of 2.2 mg/kg dose at 12-h intervals followed by 2.2 mg kg 24 h divided 12 hourly through feeding tube, was started. The Weil-Felix test was found positive at a dilution of 1:640 for OX 2, while OX 19 and OX K were negative. Two blood samples taken in two different moments and CSF were also sent to the Experimental Zoo prophylactic Institute of Sicily (IZS) in Palermo, to search for specific antibodies by indirect immunofluorescence assay. The child’s general conditions and sensorium gradually improved over 2 weeks. Chloramphenicol and doxycycline were continued for 10 days with the monitoring of complete blood counts. The child’s paired blood samples tested positive for R. conorii IgG with titres of 512 and 8192, respectively, a rise higher than 4-fold, by indirect immunofluorescence as-say. The initial bite passes unobserved, and, in many cases, the primary le-sion/inoculation scar (Tache noire) is not always present or findable as in our case. At the follow-up visit, one month after hospital discharge, the child was found in good general condition, with some residual neurological deficits such as dizziness, tiredness, and balance disturbances.

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Discussion

Rickettsia infection can cause severe complications in otherwise healthy people if the diagnosis is delayed, and the infection is not timely and adequately treated. In this section we review and separately discuss on the epidemiology, method of transmission, pathophysiology, clinical features, diagnosis, and treatment of this disease.

Epidemiology

Epidemiology of rickettsiosis is strictly related to geographic distribution of the vectors. Recent evidence highlights the consequence of global warming in the transmission of some vector-mediated diseases, resulting in an increased number of infections. Nevertheless, several other variables must be examined; in particular, migration and significant increase in international travel with related risk of importing parasites and vectors [3].

R. rickettsii is the pathogen causing Rocky Mountain spotted fever (RMSF), which is prev-alent in the American continent. In Brazil, the disease is also known as Brazilian spotted fever. It almost affects only children among 5-9 years of age [7]. Although this microorganism was first described in the Bitterroot Range of the Rocky Mountains of the Mountain State, currently only a few cases are reported in this region. The incidence of RMSF has a cyclical pattern but has generally increased in recent decades. Outbreaks of severe infections have been detected in both rural and urban areas. The severity of RMSF ranges from mild to life threatening. With improvements in supportive care and the development of effective antimicrobial therapies, the fatality rate from RMSF decreased from 30% in the mid-1940s to <5% by the mid-1950s [8].

Mediterranean spotted fever (MSF), also known as boutonneuse fever, is caused by R. Conorii, representing the most common rickettsiosis in Italy. MSF was first described in Tunisia in 1909. It is distributed over a wide geographical area that includes India, Paki-stan, Russia, Ukraine, Georgia, Israel, Morocco, Southern Europe, Ethiopia, Kenya, and South Africa. MSF cases in Europe have progressively increased since 1980 and, in some areas, prevalence is 11-26%. Epidemiological data show that in the Mediterranean basis there is a peak of cases between the months of July and August. In other regions it occurs during the warmer months when ticks are active. It has been established that high temperatures affect the incidence of the disease by modulating tick behaviour. Indeed, an experimental model performed in 2008 confirmed the increase in human affinity of the tick Rh. sanguineus when exposed to warmer temperatures, conditioning the complete development phases of the organism [9]. However, some Mediterranean countries have experienced a constant increase in the incidence of MSF over the last years [10]. Although the mortality rate is less than 3%, about 400 cases of MSF are reported every year. The most affected regions are Sicily, Sardinia, and Southern Italy [11]. Several studies reported increased mortality in patients with G6PD deficiency [12]. R. japonica was recognized as the causal agent of a febrile spotted disease encountered in Japan and the East Countries.

R. akari, the cause of vesicular rickettsiosis, also known as rickettsialpox, is transmitted by the house mouse mite. Unlike other rickettsiae which target endothelial cells, macrophages characterise an important target cell for R. akari. It was first reported in 1946 in New York City and caused vesicular lesions resembling chickenpox. Therefore, the disease caused by R. akari became known as rickettsialpox [13]. Rodents are the reservoir. It has been reported in many countries worldwide and affected children included case series from Mexico [14].

Members of rickettsiae causing typhus include R. typhi, the cause of murine typhus, and R. prowazekii, the cause of petechial or epidemic typhus. R. typhi is transmitted by fleas, whereas R. prowazekii is transmitted by human body lice or pediculus humanus corporis. It is also reported that the transmission of R. prowazekii from flying squirrel to human. The typhus cases caused by flying squirrels, not related to body lice as vectors, are known as sylvatic typhus.

Petechial or epidemic typhus is commonly considered the most virulent of rickettsial infections, with a high mortality rate even if treated. In untreated primary infection, the mortality can be up to 60%, with the highest mortality occurring in elderly and malnourished patients [15]. The human body loses only one vector because infected lice die five to seven days after they become infected. Worldwide, there are no reservoirs other than humans. Murine typhus is moderately severe and probably underestimated worldwide.

Route of Transmission

Rickettsiae responsible for spotted fever are mainly transmitted to vertebrate hosts by arthropod vectors, mostly ticks. Ticks are hematophagous arthropods and are categorized in two major families, the Ixodidae and the Argasidae, with different morphological features and feeding habits [16]. Ticks represent the hosts, reservoirs, and natural vectors of R. conorii. Ticks hosting others rickettsiae are significantly less fertile than uninfected ticks. Therefore, horizontal transmission by parasitizing from host infected animals contributes significantly to the maintenance of infections in ticks. Presently, other two ways of tick infection with rickettsia are reported. Vertical transmission occurs through transovarial transmission (from adult female tick to egg) and via trans-stadial passage (egg to larva to nymph to adult tick), thus circulating in all developmental stages [17]. Transmission occurs following a bite of the dog's brown tick, Rh. sanguineus, or other tick species such as Dermacentor, Haemaphysalis, Amblyomma, Hyalomma and Ixodes. Clusters of human cases of spotted fever, infested ticks and infected dogs imply the domestic dog as a potential vehicle of transmission. Ticks transmit the infectious agent to host humans by regurgitation of infected saliva during the meal. The pathogen R. conorii becomes virulent because of

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exposure to blood and warmer temperature. So, the longer the tick remains attached, the greater the risk of transmission.

Pathophysiology

Following the inoculation of tick into the dermis, rickettsiae adhere to the vascular endothelium through protein ligands and induce lesions in host cell membranes. Membrane damage induces endocytosis, consequently internalized rickettsiae gain access to the cy-tosol by continuous lysis of the vacuolar membranes. It is possible by using membranolytic enzymes, possibly phospholipase D and hemolysin C, to achieve phagosomal escape [18]. By active polymerization of intracellular actin performed by the pathogen, rickettsiae can easily invade adjacent cells despite minimal initial damage to host cells. Rickettsia proliferates and damages host cells by altering membrane peroxidase, activating pro-tease. The histological correlation of the initial macular or maculopapular rash consists of perivascular infiltration of lymphoid and histiocytic cells with oedema. The main target cells of R. conorii are the endothelial cells lining small and medium-sized blood vessels [19]. The presence of the infectious agent triggers an inflammatory cascade, which includes the release of cytokines such as tumor necrosis factor alpha (TNF-α), interleukin-1 beta (IL-1 β) and interferon gamma (IFN-γ). Endothelial cells infected by R. conorii induce procoagulant activity and surface E-selectin expression. The release of chemokines and the expression of vascular selectin produces the infiltration of damaged endothelial cells by lymphocytes, macrophages and sometimes neutrophils. Local inflammation and immune responses are suspected to contribute to vascular damage characteristic of rickettsiosis. Nevertheless, the benefits of an inflammatory and immune response are more effective. Indeed, it has been reported that blocking the action of TNF-α and IFN-γ in ani-mal models decreases survival and increases morbidity of infections in the spotted fever group, possibly inhibiting upregulation of nitric oxide synthetase and intracellular argi-nine-dependent killing [20]. Direct contact of endothelial cells with CD8 T lymphocytes that produce perforins and NK cells that produce IFN-γ helps to manage infection. Endothelial cells infected with rickettsia increase the expression of procoagulant molecules, the consumption of coagulation factors and may lead to disseminated intravascular coagulation (DIC).

The proliferation of rickettsiae within the cytoplasm of infected endothelial cells leads to lymphohistiocytic or leukocytoclastic vasculitis resulting in petechial rash. Ultimately, this process causes microvascular extravasation, tissue hypoperfusion and probably is-chemic damage to the terminal organs.

Clinical Features

The incubation period varies from 2 to 14 days with an average of 7 days. In about 60% of affected patients, the recent removal of an adhered tick is reported in patient history, although the site of the tick bite is usually not observable. Generally, MSF in children and adults has similar clinical features. The clinical characteristics of MSF exhibit some variability due to the different subspecies within the R. conorii described in literature. The classical triad of symptoms defining MSF is fever, maculopapular rash, and an inoculation eschar at the site of tick bite, which is observed in 40% of cases [21]. Initial symptoms are nonspecific, including headache, anorexia, myalgia, and arthralgia. Fever may exceed 40°C and may fluctuate or persist high. Headache is usually partially unresponsive to analgesics. Furthermore, fever and headache persist if the disease is not treated. Gastrointestinal symptoms including nausea, vomiting, diarrhea, and abdominal pain occur in the early stage of the disease. Typically, maculopapular rash appears 3-5 days after the onset of fever and about 5% of children may not develop any rash. Initially patients pre-sent with sparse pink or light red macules or maculopapules typically at the extremities, including ankles or lower legs, which later spread rapidly throughout the whole body, including the soles and palms, while sparing the face [22].

After several days, in approximately 10% of cases, the rash becomes petechial or hemorrhagic sometimes with palpable purpura [23]. In severe forms, petechiae can evolve into ecchymoses that may necrotize. Severe vascular occlusion secondary to rickettsial vasculitis and thrombosis are infrequent but may result in gangrene of the fingers, earlobes, scrotum, nose, or an entire limb. About 70% of patients at the site of the tick bite exhibit an indolent eschar or “tache noire” accompanying regional lymphadenopathy [23]. Despite MSF usually has a mild course without further consequences, complications have been reported in 1% to 20% of patients with a mortality rate of 3% [24]. Rickettsial infections may affect many organs, including the central nervous system (CNS). Usually, neurological manifestations include meningitis, encephalitis, and acute disseminated encephalomyelitis [25]. Patients may also experience ataxia, visual loss, seizures, and hearing impairment. In addition, it was demonstrated that rickettsiae can persist and reappear after a relatively long time in the CNS in immunocompromised mice, causing a fatal neuroinflammation [26]. CSF parameters are usually normal, however one third presents with mononuclear pleocytosis (<10-300 cells/μL) and 20% with increased protein amount (<200 mg/dl). Cardiac symptoms, including coronary ectasia and atrial fibrillation [27], renal failure [28], intraocular inflammation [29] and pancreatitis [30] have been described. Interstitial pneumonia and vascular extravasation in the lungs can lead to non-cardiogenic pulmonary oedema, meningoencephalitis can cause significant cerebral oedema.

Patients with cardiac and respiratory impairment [31], glucose 6 phosphate dehydrogenase (G6PD) deficiency [32], diabetes mellitus [33] are at higher risk of severe forms. The clinical course of severe forms of MSF is characterized by extensive thrombosis leading to renal, hepatic, and respiratory failure, requiring hospitalization in intensive care unit. Clinical features associated with a fatal outcome include neurological deficits, respiratory

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distress, acute renal failure, hepatomegaly, jaundice, and CID-like syndrome. Findings may include purpuric skin lesions and death in 1.4-5.6% of cases [34,35]. Fortunately, the disease is usually milder in children.

Diagnosis

Laboratory abnormalities are frequent but non-specific. At first, total white blood cell counts are often normal or low, but leukocytosis may develop as the disease progresses. Other types of abnormalities include differential leukocyte counts with left deviation, anemia (33%), thrombocytopenia (<150,000/μL) (33%), hyponatremia (20%) and increased serum amino transferase levels (50%). The presence of these features support the diagnosis and help to rule out some differential diagnoses. The diagnosis of a rickettsial illness has most often been confirmed by serological testing. Since no reliable diagnostic test is available to confirm acute infection, the decision to initiate treatment should be based on compatible epidemiological, clinical and laboratory features. MSF should be considered in patients presenting with acute febrile illness accompanied by headache and myalgia from spring to autumn with a recent history of tick exposure. Since half of pediatric deaths occur within 9 days of the onset of symptoms, early treatment should be considered in case of high suspicion for MSF. A rapid response to early treatment is also useful from a diagnostic point of view. Several laboratory diagnostic tools exist for the diagnosis of R. conorii infection. Serological tests are widely used for the diagnosis of MSF, which is retrospective, as there is no increase in antibodies between 7 and 15 days after the onset of the disease. The gold standard for the serodiagnosis of the disease is the indirect immuno-fluorescence antibody (IFA) assay [36], detecting antibodies indicative of Rickettsia infection. At least two serum samples collected two to four weeks apart during acute and convalescent phases of illness are required for definitive diagnosis. Seroconversion or a four-fold or greater rise in antibody titer confirms acute or recent infection [37].

Molecular techniques, as polymerase chain reaction (PCR), are useful to diagnose the illness during the first week of symptoms. Unlike serology, it can differentiate between species. PCR can be performed on both whole blood and tissue specimens, mostly skin specimens [37]. Although very specific, the sensitivity of this method is not higher than 70%. It may also be adversely affected by prior antimicrobial therapy and suboptimal se-lection of skin lesion for biopsy. PCR on blood is, however, less sensitive than PCR con-ducted on tissues since low numbers of rickettsiae circulate in the blood (<6 microorganisms/ml) [38]. Before the onset of treatment, blood samples and biopsy specimens should be collected, since sensitivity of the assay is decreased by antibiotic therapy [39]. Further characterization of rickettsial species and subspecies is possible using advanced PCR techniques and primers [40], but it does not improve the management of the disease.

Furthermore, in the presence of rash, vasculotropic rickettsiosis can be diagnosed even on the third day of illness by biopsy of a petechial lesion and immunohistochemical or immunofluorescence demonstration of rickettsia-specific antigen in the endothelium.

Treatments

Delayed diagnosis and treatment may result in increased severity and fatality. Initial diagnosis and suitable treatment should be based on a high index of suspicion and appropriate clinical features. Furthermore, epidemiological features and laboratory findings are important adjuvants. The antibiotic therapies for MSF that have demonstrated efficacy over time are tetracyclines and chloramphenicol. Although efficiently treated with tetracycline, doxycycline, chloramphenicol, ciprofloxacin, ofloxacin, levofloxacin, azithromycin or clarithromycin, the treatment of choice for MSF remains the administration of doxycycline, which is a second-generation tetracycline, highly effective and easily accessible. Doxycycline dosage is 2.2 mg/kg/day every 12 hours (max 200mg/day) [41]. The pharmacological treatment should be continued for a minimum of 5-7 days and for at least 3 days after fever resolution to avoid recurrence, especially in patients treated early. Patients treated usually become afebrile in 48 hours, so the duration of therapy is usually less than 10 days. As studies have demonstrated that even one-day courses of treatment with one or two doses of doxycycline seem to be as effective as longer courses [42]. Although tetracycline and doxycycline may be associated with tooth discoloration in children under 8 years of age, recent studies demonstrated that administration of short courses of doxycycline (up to 21 days) to children under the age of eight neither seems to darken the shade of the teeth nor to cause visible staining [43,44]. An additional benefit of doxycycline is its efficacy against a potential concomitant infection with Ehrlichia.

Most infections resolve quickly with appropriate antimicrobial therapy without re-quiring hospitalization or other supportive care. Severe infections sometimes require hospitalization in intensive care units. Macrolides are also efficient and safe alternatives reserved for patients with doxycycline allergy, as they reach high intracellular concentrations [45]. Therefore, clarithromycin, azithromycin and josamycin can all be equally used in children and adults. Chloramphenicol has also been used as an alternative to doxycycline for the treatment of MSF, nevertheless the toxicity associated, and the described relapses have restricted its use [46]. Once compared to treatment with tetracycline, the administration of fluoroquinolones demonstrated increased MSF severity and longer hospital stay [47].

In addition to the study of the molecular basis of rickettsial immunity, Chan et al has revealed that the administration of anti-rickettsiosis monoclonal antibodies could lead to the killing of R. conorii in rodents through complement activation [48]. This potential future treatment prospect could represent an excellent alternative to antibiotic treatment in case of antibiotic resistance or contraindications to the use of antibiotics.

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Conclusions

The Rickettsial infection is a disorder which can have severe clinical and neurological implications. Precocious differential diagnosis is not easy if local outbreak episodes are unknown, or the skin manifestations are not striking. Early diagnosis and targeted treatment help to manage the affected people and are worthwhile to prevent complications.

Author Contributions

Conceptualization, G.N., M.C., G.N., G.C. and P.P.; methodology, G.M.C; software, G.C.; validation, P.P; data curation G.M.C and G.C. S.M.; writing-original draft preparation, G.M.C. ; writing-review and editing, M.C., P.P. and G.C. ; visualization, G.M.C ; super-vision, S.M, G.N. All authors have read and agreed to the published version of the manuscript.

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