Clinical Aspects of Tickbite Fever - The Form of Tick Typhus Occurring in Southern Africa — Prof JHS Gear

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Curriculum vitae

James HS Gear was born in 1905, grew up and was educated on the Witwatersrand. He qualified in medicine in 1929 at Wits. In 1930 he joined the SAIMR, and he retired as their Director in 1973. After a fellowship which took him to London School of Tropical Medicine, he instituted the post-graduate course for the Diploma in Tropical Medicine and Hygiene at Wits. His research in producing vaccines was internationally accepted. During the earlier years his involvement in the SA Medical Corps he played a major role in successfully ending epidemics, and he subsequently established yellow fever and typhus fever vaccine laboratories at the SAIMR - over 5 million doses of typhus vaccine were produced and used all over Africa and as far as Russia. Over the years he was instrumental in producing influenza virus vaccine, poliomyelitis vaccine, a vaccine against Newcastle disease of fowls, vaccines against measles and his work on the Coxsackie B virus was highly regarded internationally. His other interest was in immunological disorders and his research in this field helped to understand better many previously obscure conditions; it is also of particular relevance to our understanding of certain cancers and in this era of organ transplantation, graft acceptance and rejection. Dr Gear served for many years on the Prime Minister's Scientific Advisory Council, on the Council of the MRC, the State Health Council, WHO-study groups and on many more. Dr Gear's work in tropical medicine, virology and immunology was honoured with many prestigious awards, in South Africa and abroad.

Summary

Tickbite fever, as it is being experienced today in southern Africa, is clearly described, considering all clinical aspects like the history, incubation period, complications, systemic manifestations, diagnosis, prevention and treatment. Early diagnosis is of great importance and highly effective treatment is available today; no patient should now die of tickbite fever.

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Tickbite fever, the variety of tick typhus occurring in southern Africa, is caused by *Rickettsia conori var pijperi*, and transmitted by ixodid ticks which include the common veld ticks - species of *Amblyomma* and *Rhipicephalus*, and the dog ticks - *Haemophysalis leachi* and *Rhipicephalus sanguineus*. Veld rodents including the striped mouse, *Rhabdomys pumilio*, and the vlei rat *Otomys irroratus* are often infected in nature and may serve as reservoir hosts infecting lines of ticks previously free of the infection. However, the infection is passed through the egg, from one generation of ticks to the next, each stage of which, the larva, the nymph and the adult are infected and infective, being capable of transmitting infection to their human hosts. Most infections are transmitted by larval ticks which are so small, being pinhead size, that they are not seen or felt, and are able to attach and feed and thus transmit the infection.

The rickettsiae are obligate, intracellular parasites, relying on the enzyme systems of their host cells to a large extent for their metabolism and multiplication. They parasitize the endothelial cells of the blood vessels, particularly of the capillaries. Here the infection gives rise to typhus nodes, the unit lesion of rickettsial infections, which are formed by the adherence of platelets and white cells to the infected endothelial cells and by an infiltration of inflammatory cells consisting of mononuclear cells, lymphocytes, a few neutrophil leucocytes and occasionally an eosinophil leucocyte. These typhus nodes are scattered throughout the vascular system and are particularly numerous in the skin where their presence gives rise to the characteristic rash, and in the brain where their presence gives rise to the characteristic severe headache and delirium, and in severe cases to stupor and coma.

Clinical Picture

History

Most patients who develop tickbite fever give a history of visiting the bushveld or other rural areas where ticks abound. Ticks may survive for many weeks on clothes and blankets and they may transmit the infection some time after they were first picked up on the veld, and so on occasion the incubation period may seem to be unduly prolonged. Other patients will tell of deticking their dogs, and sometimes while crushing the ticks between their thumb and fingers, or between their thumbnails, recalling the blood spurted into one of their eyes. Many patients contract tickbite fever in the suburbs of the cities and towns, and will tell of allowing their tick-infested dogs inside the house and into their bedrooms, often to

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sleep on their beds or in the baby's cot. It is not surprising to find that cases of tickbite fever frequently occur in such households.

Incubation Period

The incubation period, from the time of the tick attachment and infection to the onset of general symptoms, is usually about one week. Often a patient presenting in a doctor's consulting room on Monday morning will tell of a visit or a picnicking or camping expedition the previous weekend into the country or bushveld where ticks are prevalent. He may complain of irritation caused by numerous tickbites, especially on his lower limbs, but more often the patient is unaware of the infecting bite. During the incubation period of the systemic illness, one or more of these tickbites, the infective tickbite, will develop first into an inflamed red papule, the centre of which then becomes necrotic and black to form the characteristic primary sore or *tache noir* of tickbite fever. It may be situated anywhere on the surface of the body, but in adults and older

Highly effective treatment for tickbite fever is available

children is most often found on the lower limbs, in the groin or on the lower abdomen. In infants and babies it is often on the scalp where it may be difficult to detect because of the hair and relatively dense tissues of the scalp. A clue to the whereabouts of the primary sore may be given by finding painful lymph glands draining the area. These glands become enlarged and tender but the bite mark itself is usually painless. Often a patient complaining of enlarged tender glands is unaware of the presence of the bite lesion. The primary sore with its black centre is the most typical and diagnostic sign of tickbite fever and is present in most cases. However, in some patients, in spite of a diligent search it cannot be found. In others the

Early diagnosis is of crucial importance

infection occurs through the conjunctivae which may become infected by rubbing with contaminated fingers or by a spurt of blood while crushing a tick. The affected eye becomes inflamed and the lids may become so swollen that the eye cannot be opened. The regional lymph gland draining the eye tissues, the pre-auricular gland, becomes enlarged and tender, and the signs and symptoms of systemic infection may then develop.

Systemic manifestations of tickbite fever

The first general symptom of tickbite fever is a feeling of unusual tiredness and malaise noted in the evening. The following morning the patient may feel better but that evening he feels worse and experiences chills, muscle and joint pains and headache, and slight anorexia, and develops fever. The fever reaches its height on the second or third day and in typical untreated cases continues for ten days, with the temperature chart showing an intermittent or remittent course. In mild cases the fever may last from one to seven days, with little constitutional disturbance. In severe cases, in the absence of specific treatment, it may continue with slight remissions for fourteen days or even longer, terminating by rapid lysis. During the fever the outstanding symptom of which the patient complains is an excruciating headache. In some patients it is so severe they say they will go mad if it is not relieved, and indeed they often become delirious. The delirium is worse at night and the patient may have visual hallucinations, seeing weird objects on the ceiling. In very severe cases the patient becomes stuporose and may lapse into coma.

On examination during the first week of illness, in addition to finding the primary sore and regional lymphadenitis, it will be noted that the patient's face is flushed, the conjunctivae congested, the tongue

Ticks may survive for many weeks on clothes and blankets

coated and the throat often slightly inflamed, associated with some cervical lymphadenopathy as part of a slight general lymphadenopathy. The heart rate is not greatly increased and indeed there may be bradycardia relative to the temperature. In mildly or moderately ill patients the abdomen is not distended and the spleen and liver not palpable although there may be slight tenderness in both upper quadrants and there may also be tenderness of the muscles of the limbs. On the third to the fifth day of illness a maculopapular rash erupts, first on

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the extremities then on the trunk. It appears in crops and new macules and papules may be noted each day for one to three days. The papules may be felt as small, shotty nodules in the skin. At first they are pinkish but later become darker. The rash is centrifugal, characteristically involving the palms of the hands, the soles of the feet and to a lesser extent the face. The profuseness of the rash

Often the patient is unaware of the infecting bite

is directly related to the severity of the illness. In mild cases only a few raised, red papules, more evident on the limbs than on the trunk may be seen. In severe cases a profuse maculopapular rash covers the whole body and the skin has a dusky, cyanotic hue. In very severe cases the rash may become haemorrhagic with bleeding into its elements associated with numerous petechial haemorrhages in the skin which may become oedematous. On recovery, especially after specific treatment, the rash rapidly resolves, but if it had become haemorrhagic, staining of the skin may be seen for some time in convalescence.

Course and Complications

In most young patients the disease, even when untreated, follows a relatively benign course, and they make an eventful recovery. Occasionally in infants, rarely in adolescents and young adults, but often in middle-aged and elderly patients, the disease tends to be severe and if the diagnosis is not made in time and specific treatment instituted, the patient may develop serious complications. In the absence of treatment complications are common in older patients and may be fatal.

Tickbite fever is essentially a disease of the blood vascular system and most complications result from vasculitis. The most frequent is deep vein thrombosis involving the deep veins of the leg and usually becoming apparent late in the course of the illness or early in convalescence. It may be further complicated by pulmonary embolism, which may be fatal. Marked varicosity of the veins may later develop as a sequel to the obstruction of the flow of blood through the leg. The retinal veins may be affected by lesions analagous to the typhus nodes resulting in defective vision of the affected eye. These lesions usually resolve without permanent damage.

In mild cases little change in the blood pressure is noted but in severe cases there may be a significant fall and the skin assumes a dusky, cyanotic appearance. The circulation may become so poor that gangrene of fingers and toes may ensue, later requiring amputation of the affected digits. In severe cases signs and symptoms of myocarditis frequently occur and death may ensue from circulatory collapse and cardiac arrest. Among the rarer complications is the development of a haemorrhagic state, with bleeding from the mucous membranes manifesting as epistaxis, haemoptysis, haematemesis and melaena and petechial haemorrhages into the skin with a haemorrhagic rash. This haemorrhagic state is associated with a marked fall in the platelet count and prothrombin index, and evidence of an incipient consumption coagulopathy. In some severely ill patients liver function may be markedly disturbed manifesting with jaundice with increased levels of blood bilirubin and markedly raised hepatic enzymes. They may also develop severe kidney disorder reflected by rising blood urea and creatinine levels and kidney failure requiring dialysis in an intensive care unit. Some patients with these severe complications may die, but others, although desperately ill, respond to treatment and are discharged from hospital relatively well. However, with the specific treatment now available, provided the diagnosis is made in time, no patient should die of tickbite fever.

Tickbite fever in young children is usually a mild disease with no complications. However, recently several cases in which the patient was severely ill were seen in the Johannesburg Hospital. These patients, soon after admission to hospital, lapsed into a comatose state associated later with

The primary sore with its black centre is the most typical and diagnostic sign

epileptiform convulsions. On the diagnosis of tickbite fever being made clinically and confirmed by laboratory tests, they were given specific treatment and also treated for their epileptiform convulsions, after which they gradually recovered consciousness but were found to have lost their power of speech. One patient, a three year old, recovered over the course of two months,

apparently re-learning the use of words from the beginning. Another patient aged five years gradually improved his vocabulary until, after six months, he had fully regained it. A third patient, a baby of eighteen months, became deeply comatose and developed gangrene of several toes and fingers and also lost the power of speech. However, after specific treatment, he recovered consciousness and apart from losing the tips of the distal phalanges of his hands and feet which were affected by the gangrene, has made a complete recovery.

Clinical Diagnosis

The clinical picture of tickbite fever is well known, indeed the signs and symptoms of tickbite fever are so characteristic that there is usually little difficulty in diagnosing the condition on clinical findings. Indeed, for specific treatment to be instituted early, in most cases the diagnosis must be made on clinical findings. However, if facilities are available, diagnosis may be confirmed in the laboratory by demonstrating rickettsiae in skin biopsies of the papules of the rash by the immuno-fluorescent technique. This is rarely possible in present circumstances.

A number of conditions characterized by a primary lesion associated with regional lymphadenitis and followed by systemic manifestations have to be considered. These include septic sores due to staphylococcal and streptococcal infections of traumatic scratches, cuts and other insect bites. Some spiders, such as *Loxocseles* and *Ciracanthium* produce necrosis of the skin and a black lesion, often with vesiculation followed by black crusting which may resemble tickbites. The lesions of cutaneous anthrax and the primary lesion of sporotrichosis, which may develop at the site of a scratch on the skin, may suggest the primary lesion of tickbite fever, but the exudate is purulent and on direct microscopy the characteristic bacilli or fungal elements will be seen. The primary chancre of Rhodesian sleeping sickness is typically associated with enlarged tender regional lymph glands and the development of fever, as occurs in tickbite fever. However, the chancre of trypanosomiasis is larger and on a white skin has a heliotrope colour and does not usually develop the central black necrotic area typical of tickbite fever,

In young children usually a mild disease with no complications

although on occasion it may do so. The primary lesions of the venereal diseases, *herpes genitalis, lympho-granuloma venereum,* chancroid and syphilis may be mistaken for that of tickbite fever. More frequently the primary sore of tickbite fever, when on the genitals, is mistaken for that of one of the venereal diseases, a mistake which may lead to unnecessary treatment and unhappiness.

In regard to the systemic manifestations of the disease, conditions causing fever and rash have to be considered in the diagnosis. The features of the rash, the time of its appearance, its distribution and the characteristics of its elements are of differential value. In meningococcal septicaemia, the rash develops on the first day of illness and is frankly haemorrhagic, but in children may be maculopapular. It is vital that tickbite fever should not be confused with meningococcal septicaemia for the latter requires urgent specific treatment. The rashes of the acute specific fevers, including rubella and varicella are usually easily recognized and should not be mistaken for that of tickbite fever. Coxsackie A and echovirus infections usually occur in infants and are characterized by a short fever, a maculopapular rash which may become slightly vesicular. The greatest difficulty may be experienced in distinguishing the arbovirus infections from tickbite fever. In South Africa these include West Nile fever, Sindbis fever, chikungunya fever and Congo fever, and they, like many cases of tickbite fever, are acquired in rural areas and in the bushveld. Like tickbite fever they present with myalgia, headache and photophobia and fever, which is often biphasic and lasts about one week. The patient's face is suffused, eyes are congested and a maculopapular rash appears on the third to the fifth day of illness. In both arbovirus infections and tickbite fever there may be general lymphadenitis but in the former the primary lesion and associated regional lymphadenitis are not found. The papules of the arbovirus rash tend to be pink and more clearly defined than the dusky papules of tickbite fever, and often have a pale halo. It is usually possible by carefully noting the features of the rash to differentiate tickbite fever from the others.

In Marburg virus disease the patient may give a history of an insect or other arthropod bite but there is no primary eschar and the rash, which is

morbilliform, develops on the fifth day of illness and may be followed by the development of a haemorrhagic state, and thus may present difficulty in differentiation from severe haemorrhagic cases of tickbite fever. Although it is usually possible on clinical grounds to distinguish tickbite fever from other conditions causing fever and rash, the final identification of the cause of the patient's illness depends on the results of the laboratory investigations.

Specific diagnostic tests

The diagnosis of tickbite fever may be specifically confirmed by demonstrating the presence of rickettsiae in skin biopsies taken from the papules of the rash by the immunofluorescent technique. As already noted the facilities for carrying out this test are rarely available to the general practitioner. When available it is possible to obtain laboratory confirmation of the diagnosis as soon as the rash appears.

The diagnosis may also be specifically confirmed by the isolation, identification and characterization of the causative rickettsiae and by the inoculation of the patient's blood intraperitoneally into guinea pigs. As this can only be carried out in a specialist laboratory and as it takes several weeks for completion it is not of value as a routine procedure. It is of value in differentiating tickbite fever from the other infections of the typhus group. In practice the diagnosis usually depends on serological tests to demonstrate the appearance of antibodies, either in the Weil Felix test, a screening test, or in the more specific complement fixation and immunofluorescent antibody tests. As these tests may not give positive results until convalescence the diagnosis has to be made on the clinical picture.

Treatment

Patients with tickbite fever are not infectious and their isolation is not necessary. Treatment of the severe headache is indicated and it may be alleviated by the administration of aspirin or other analgesics. However, the headache as well as the other signs and symptoms respond within 48 hours of the institution of specific treatment with tetracycline antibiotics. The initial dose is 25mg per kg, followed by a daily dose of the same amount divided into four doses given every six hours or three doses every eight hours, and continued for one further day after defervescence. As a rule little change in the patient's condition is seen during the first 24 hours, but 48 hours after beginning treatment there is a dramatic improvement. The patient looks better, feels better and indeed is better, and the rash fades rapidly. In severely ill patients when treatment is begun late, the response may take longer than 48 hours, but even in the most severe cases although delayed, recovery usually takes place.

Patients with renal failure resulting in oliguria and anuria may require dialysis and admission to an intensive care unit. On responding to specific treatment renal function is usually restored. If treatment is begun early no patient should now die of tickbite fever, emphasizing the crucial importance of early diagnosis.

Prevention

Tickbite fever may be avoided by not visiting the bushveld and other rural areas where ticks abound and in urban areas not allowing tick-infested dogs or cats inside houses, especially not into bedrooms. When de-ticking dogs, the person should use forceps and place the ticks into an antiseptic solution immediately. It is also advisable to wear gloves. In practice it is found that most individuals readily accept the risk of tickbite fever on their visits to the rural areas and by allowing their dogs inside, perhaps knowing that if they should contract the infection, highly effective treatment is available.