Enigma of Emerging Typhus in Jaffna – A Public Health Challenge

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1. Introduction

There is a remarkable increase in reporting of typhus cases in Sri Lanka in the recent past. In 1999, 48 cases were reported but in 2009 it increased up to 1200 cases. The people in Jaffna are well aware about typhoid but not about Typhus. Typhus caused high mortality in the past; and there is a misconception about prevention and control of typhus in Jaffna district. The above topic was chosen for the chairperson address with a view to enlighten the audience regarding typhus and to clear the misconception regarding control and prevention of typhus.

The name "Typhus" came from the Greek word for "hazy" and is given for the stupor that is seen in severe cases of epidemic typhus. Typhus fevers were prevalent during crisis situations like wars, famine and great migrations and have caused massive mortality (Cowan 2000). Typhus had been one of the greatest killers of people in recorded history. It was suspected of having been responsible for the Athens plaque during the 5thCentury B.C and the disease was recognized in 16th Century by presence of fever and rash.

For many years rickettsiologists have had the risk of losing their lives to this potentially hazardous disease. The three pioneer scientists contacted this infection while researching this disease- Ricketts,Von Provazek and Nicolle. Unfortunately Ricketts and Von Provazek died of Typhus infection and only Nicolle survived to collect the Nobel prize in 1928. It was an emerging infectious disease all over the world. As it is a potentially hazardous organism, it probably could be used in Bioterrorism as biological weapon.

Rickettsial fevers are acute bacteraemic illnesses characterized by fever and rash, spread by insects. Sometimes a small black eschar is formed at the site of insect bite. They are caused by members of the Genus Rickettsia. Rickettsial organisms are Gram negative intracellular bacilli or cocco bacilli. The species of the genus rickettsiae have been sub divided into three groups of antigenically related microorganisms, namely the scrub typhus group, typhus and spotted fever group (SGF) (La Scola and Raoult 1997). All these rickettsial organisms are transmitted through different arthropode vectors. Rickettsiae get into the blood vessels where rickettsial organisms proliferate on the endothelium of small blood vessels and releases cytokines which damages the endothelial integrity with consequent fluid leakage, platelet aggregation and proliferation of polymorphs and monocytes which lead to occlusive endangitis and causing micro infarctions in skin, lungs and kidney. The complication may vary depending on the species. However, main complications are meningo encephalitis,DIC and interstitial pneumonia

Scrub typhus was first described in Japan and was a major cause of febrile illness in Asia and Pacific regions. It was an ancient disease and caused by *Rickettsiae tsutsugamushi*, which was recently renamed *Orienta tsutsugamushi* of which antigenic types of three prototype strains Gallian, Karp and Kato are well known. This organism was removed from the genus rickettsia and moved to the new genus because of significant differences in 16s rRNA and cell wall structures which lack lipopolysaccharide and peptidoglycan typical of other members of the genus, (Kelly,2002). Antigenic types such as Shimokoshi, Kawasaki and Kuroki, are different from the initially described prototype strains. The causative organism is transmitted to humans through the bite of larval trombuculid mites, living on waist high imperata grass growing in previously cleared jungles around villages and in plantations.

The typhus group includes epidemic (louse-borne) typhus and murine (Flea-borne) typhus. Epidemic typhus is transmitted by the human body louse, *Peduculus humanus* from active

human cases or from healthy or sub clinical cases. In outbreaks in the Burundi prison in 1995, infection spread among malnourished inhabitants, causing over 50,000 cases with a mortality of 2.6%. Murine typhus is also called rat flea typhus. The bacteria naturally resides in rats, mice and other rodents and are transmitted to humans via the bite of fleas which live on rodents.

The spotted fever group (SFG) rickettsiae includes more than twenty species. Among them 16 species are found to cause human rickettsioses. Other species of SFG found only in ticks with no known pathogenicity towards human. They are mainly transmitted through ticks of dog, cattle, rodents and wild animals. It caused 30% of mortality in pre-antibiotic era.

2. Diagnosis of rickettsial infections

Although there are many recent developments in the laboratory diagnosis of typhus, careful clinical examination and epidemiological investigations remain important for diagnosis. As these are potentially hazardous organisms, only research laboratories that have level 3 containment facilities and extensive personal experience in cultivating rickettsia were able to involve in isolating rickettsia from clinical specimens.

The Weil-Felix test is the simplest and commonest test used in poorly resourced countries where more sophisticated facilities are not available. Antigens from the proteus strains *P.vulgaris,* OX-2 , P.vulgaris OX-19 and *P.mirabilis* OX-K are used. This test is based on serological cross-reactions between the two genera. This test is however negative in upto 50% of cases. Although this test lacks sensitivity and specificity, it has historically been used for laboratory diagnosis.

Lack of a group specific antigen confers an inherent limitation for most existing serological assays. Each assay is limited by the detectable antigen. Testing the sera against different species using multiple IFA or Immunoperoxidase is therefore an essential component of laboratory diagnosis.

Rickettsia may also be detected by PCR amplification from a variety of samples that includes blood, skin, biopsy samples and arthropod tissues. Moreover, this method is useful when immunological techniques or isolation of the causative agent is difficult. (Furuga 1993).

3. Treatment of Typhus

Typhus responds to tetracycline or doxycycline very well. As these drugs are having side effects, chloramphenicol is used in children.

4. Rickettsiosis in Asia & Sri Lanka

Sri Lanka was described as one of the risk areas for scrub typhus (Cowan, 2000). In 1938 two cases of 'urban typhus' were diagnosed by Weil-Felix reaction at General hospital, Colombo. This was assumed to be the first report of murine typhus in Sri Lanka. Van Peenen *et al* (1976*)* reported that scrub typhus was not a major public health concern in Sri Lanka on the basis of a 6% prevalence rate in a sero-prevalence study in the Colombo district. In 1995, Vasanthathilaka and Senanayake, and in 2003 Amarasinghe et. al described the murine typhus in Sri Lanka. However, specific serological tests were not carried out on these studies.

In Sri Lanka, typhus like fevers had been often diagnosed clinically. One important clinical criterion for the diagnosis of typhus by Sri Lankan clinicians was the rapid recovery noted with tetracycline or chloramphenicol. Sporadic outbreaks of such fevers have been diagnosed using only clinical criteria due to unavailability of specific diagnostic tests in Sri Lanka. The Weil-Felix test, though known to be non specific and of low sensitivity is the only test available in Sri Lanka. Absence of readily available tests of high specificity and sensitivity is a limitation when laboratory confirmation of the clinical diagnosis is required. In addition, many aspects of the disease including specific aetiology, epidemiology and suitable preventive measures cannot be studied in the absence of a suitable diagnostic test.

5. Study in Nawalapitiya

In July 2001 - June 2002 there was a study conducted by Nagalingam *et.al* at District General Hospital Nawalapitiya, where all the patients presenting with fever and rash were included. Apart from fever and rash, other signs exhibited were arthralgia (32%),

headache (4.8%) and vomiting (2.4%) among the 53 patients. None of the patients had hepatomegaly or lymphadenopathy. All the patients were followed up for a period of 3 years and there were no relapse or complication observed.

An erythematous maculopapular rash was the most characteristic feature of the illness and found in all the patients. The rash involved the face, trunk, limbs, palms and soles in majority (76.5 %) of the patients. No patient developed haemorrhagic / purpuric rash which is supposed to be associated with several rickettsial infections. Duration of fever on presentation to the hospital ranged from 2-15 days with a mean of 6.22 ±2.99. Majority of the patients (86%) were below 6 years of age. Increased admissions were noted from December to March each year (75%).

As there is no specific diagnosis available in Sri Lanka, Serum samples were freeze dried and sent to the Reference Laboratory (RRL), France where serological diagnosis using IFA, Western blot and cross adsorption studies carried out. Serum specimens were tested using 13 rickettsial antigens which include SFG(*R.conorii* Indian, *R.japonica, R .helvetica, R.slovaca,* AT1 Rickettsia, *R.felis, R.heilongjiangii*) ,Typhus group (*R.typhi*) and Scrub typhus *O tsutsugamushi* strains (Gillian,Kato,Karp and Kawazaki). All the positive sera had very high titers to *R.helvetica, R.japonica, R.felis R.honei.* and *R.slovaca.* Western blot assays and cross adsorption studies revealed they are mainly *R honei* , *R felis* and some were undetermined.

6. Study in Kandy

A study conducted by Kularatne *et al* during the same period in January 2000 to December 2001 in Kandy shared similarities and differences with this study. In their study serological testing was done in 2 Reference Laboratories in Thailand and Japan, these workers demonstrated a positive antibody response to the antigens of SFG *O tsutsugamushi* and *R typhi* in their cohort of patients, the results of both studies show clearly that rickettsial disease, in particular due to SFG group of rickettsiae is prevalent in the areas from which the patient populations lived and/or worked.

Serological tests are limited in several ways. The absence of a group antigen means that antisera to individual species are required for precise aetiological diagnosis. However, even when such antisera are available, cross reactions between different species limits the usefulness of these tests (Raoult and Roux 1997; Raoult and Dasch 1987).

Therefore in 2004 Nagalingam *et.al* developed a reckettsial genus specific PCR test in which all the typhus cases other than scrub typhus can be detected. Also, the results can be obtained within 24 hours and 1ml of single blood sample is enough to perform the test. It can be used for mapping of rickettsial disease in Sri Lanka.

7. Mapping of rickettsial disease in Sri Lanka

A study was done by Nagalingam *et.al* in 2004 to map the rickettsial disease in Sri Lanka. In this study, samples from all 9 provinces were collected and screened by genus specific PCR and scrub typhus ELISA. In this study Northern, North central, Eastern, North Western and southern province were positive for scrub typhus; Central province was positive for SFG and Sabragamuwa and Uva provience were positive for both scrub typhus and SFG. None of the samples were positive in Western province. From Northern province all ten samples tested were received from Jaffna Teaching Hospital and were only positive for Scrub typhus.

8. Study on Typhus in Jaffna

Nagalingam *et.al* conducted a study in Jaffna Teaching Hospital from December 2004 – November 2005 where 46 patients were included in the study. Seasonality pattern was noted with high number of cases from December to March. Mean duration of fever was 6.3±2.6 days. All the patients presented with fever and responded to doxycyclin. Majority of the patients had eschar. None of them had rash.

Nine patients' samples were tested for spotted fever and scrub typhus. All 9 were positive for scrub typhus and negative for spotted fever.

Further research studies should be carried out in all the suspected Typhus cases presenting to Jaffna Teaching Hospital by using the Genera specific PCR and scrub typhus ELISA IgG and IgM. Also the risk factors for scrub typhus in Jaffna to be studied.

9. Seasonal Variation

A seasonal variation was observed with increased admissions between December to March in all the studies. The climatic condition from December to March may have an influence on the ecology of vectors responsible for transmitting rickettsiae. Seasonal variation of Rickettsial diseases may be related to the characteristics of vectors. Halim *et al* (1983) have investigated the seasonal variation of some vectors such as ticks in Sri Lanka. There is also a generally held assumption that all the vectors have a seasonality pattern in their natural setting. Seasonal variation may also be a result of changes in human-vector interaction due to changes in human behavior.

In 2010 January to March period there were 63 cases reported from Jaffna district. Reasons for increasing trends of typhus fever are not known but there have been important changes on conditions that bring human to contact with rickettsia infected larval mites. This may become to actual increase in the number of mites or more likely increased human contact with the habitat of infected larvae. In 2008 and 2009 high numbers of cases were found to be in Kopay, Manipay and Tellipalay area.

All the studies in Jaffna revealed that the scrub typhus is the prevalent disease and its vector is mite. Some authorities responsible for the control of typhus in Jaffna appear to think that it is a tick-related disease and direct the health team and the public to control ticks in domestic animals. Any meaningful program to prevent scrub typhus should concentrate on mite control.

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