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CLINICO-LABORATORY PROFILE OF SCRUB TYPHUS IN CHILDREN

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ABSTRACT

Aim : To study the different clinical and laboratory features of scrub typhus in children aged 1-12 years.
Study design & methods : This is a retrospective study using case records. This study was conducted in Sri venkateshwaraa medical college & research centre, Ariyur, Pondicherry. All diagnosed cases of scrub typhus admitted to paediatric ward during the period 2011-2012 were analysed .Diagnosis was based on positive IgM Elisa.
Results: Twenty six patients were diagnosed with scrub typhus over the one year period(2011-2012).Fever, toxic appearance, tender hepatomegaly were the commonest clinical features and noticed in 100% ,76.92% & 76.92% respectively. Other clinical symptoms are vomiting (57.69%), cough (39%),abdominal pain (19.23%), headache (15.38%) & redness of eye. An ulcer with white necrotic base along with tender enlargement of draining lymph node was present in 65.38%. Four patients presented with typical black eschar. Thrombocytopenia is the commonest haematological abnormality and was present in more than half of the patients. Elevated liver enzymes was noticed in 76.2% of patients. Leucopenia and interstitial infiltrates in X-ray are other laboratory abnormalities. Positive weil-felix test was noticed in 20 of the 26 confirmed cases with IgM Elisa. None of our patients had complications all responded dramatically to doxycycline .In all of our cases doxy had been started before the reports.
Conclusion : Scrub typhus should be considered in the differential diagnosis of acute febrile illness in and around Pondicherry especially rural areas. Empirical therapy with doxycycline is life saving awaiting reports .High suspicion and searching for an ulcer or eschar should be done in all patients with fever .

KEYWORDS

Background: Scrub typhus is becoming increasingly common in Paediatric patients. In many of our Indian settings it is not possible to diagnose scrub typhus by laboratory means. Hence it becomes essential to make a clinical diagnosis early based on the initial symptoms and signs as earlier diagnosis and treatment with doxycycline will prevent life threatening complications. This study aims to highlight the clinical and laboratory manifestations of uncomplicated scrub typhus as many of the previous Indian studies were on complicated paediatric scrub typhus.

Objective : To study the clinico-laboratary profile of scrub typhus in children aged 1-12 years admitted in our hospital

Type of study : It is a retrospective study by using case records

Inclusion criteria: patients diagnosed as scrub typhus by positive IgM Elisa were included in the study

Material and methods: This retrospective study was conducted in sri venkateshwaraa medical college and research centre, a tertiary care centre located in Ariyur, Puducherry, India. Twenty six cases of paediatric scrub typhus serologically confirmed with IGM Elisa were reviewed .Epidemiological variables like age, sex, locality were taken into account .Among the clinical features fever, cough, vomiting, abdominal pain, headache, diarrhea, regional lymphadenopathy, toxic appearance, eschar or ulcer , skin rash, hepatomegaly, splenomegaly were predominantly considered. Blood haemoglobin, total leukocyte count ,differential count, platelet count, ESR, LFT, RFT and x.ray chest were done in all the cases. weil felix test was done in all the cases and IgM Elisa was the confirmatory test used.

Results: Among the twenty six confirmed patients fever was the most consistent symptom and was present in all the patients. The next common clinical features are toxic appearance that was there in 76.92% of patients. Hepatomegaly which was tender was present in 76.92 % of patients and 57% of patients had splenomegaly. Isolated splenomegaly was seen in 3 patients. An ulcer with a white necrotic base was seen in 65.8% of the children which represents the entry site of organism .only one of our patient had a typical black eschar. Children less than 6 years constituted 61.53% of patients. Remaining patients were in the age group of 7-12 years. Of the 26 patients 16 were male and 10 were female. In 11 of our patients haemoglobin was less than 11.5gms% .The total count was less than 4000 /dl in 4 patients and more than 11000/dl in three patients, rest of the patients had a normal count. Mild thrombocytopenia was noticed in half of the patients (13 patients) and 2 patients had moderate thrombocytopenia. None of the patients had severe thrombocytopenia. AST and ALT were elevated in 20 of the 26 patients.20 patients had trace to 1+ albuminuria. Of the 26 patients confirmed,20 showed a significant positive weil felix test also.13 patients had hypoalbuminemia.

Age & sex distribution of patients

AGE	1year to 3years	6
	3years to 6 years	10
	6years to 12 years	10
SEX	Male	16
	Female	10

Clinical features	No of patients	Percentage
Fever	26	100
Cough	10	39
Vomiting	15	57.69
Abdominal pain	5	19.23
Headache	4	15.38
Diarrhea	2	7.69
Regional lymphadenopathy	17	65.38
Toxic appearance	20	76.92
Skin ulcer or eschar	17	65.38
Skin rash	2	7.69
Hepatomegaly	20	76.92
Splenomegaly	15	57.69
Crepitations in lungs	3	11.53
Weil-felix test	21	80.76

Discussion:

Scrub typhus is a zoometric febrile illness caused by a gram negative bacterium Oriental tsutsugamushi. Historically the disease is known to occur in military camps. The disease derived its name from Japanese, called tsutsugamushi (from tsutsuga meaning dangerous and mushi meaning insect or mite). The disease apart from scrub vegetations occurs in regions of sandy beaches, mountain deserts and equatorial rain forests also. Moreover scrub typhus which was considered to be a disease of rural area is now being increasingly found in urban dwellings also. [9]The disease peak usually during the rainy months September to February.[9]

Scrub typhus is endemic in southeast Asia and western pacific islands. In India it is found in the Himalayan belt and the coastal areas of south India. In India rickettsial infections have been documented in Jammu and Kashmir, Himachal Pradesh, Uttaranchal, Rajasthan, Assam, West Bengal, Maharashtra, Kerala, Tamil Nadu and Delhi (1,2&7).In one study conducted in Delhi serological evidence of scrub typhus was found in 48% of population and rodents act as the main reservoir[5].

In children in whom it was considered nonexistent is becoming common nowadays .So in evaluating a child with fever scrub typhus should be considered in the differential diagnosis since serologic surveys suggests that as many as one-half of cases of scrub typhus might be in children.[4].Also clinical manifestations of scrub typhus in children are not typical and it is different from adult patients. Further the occurrence of eschar which is considered pathognomonic and appearance of trunkal rash will not be there always.

Oriental tsutsugamushi is a small (0.3 to 0.5 by 0.8 to 1.5 µm), gram negative bacterium of the family Rickettsiaceae .It is an obligate intracellular organism. The cell wall of Oriental lacks lipopolysaccharide and peptidoglycan and does not have an outer slime layer. The cell wall comprises of integral outer membrane proteins like major surface proteins (56kDa) and some minor surface protein (110, 80, 46, 43, 39, 35, 25 and 25kDa). The 56 KDa OMP is type specific and it is the target antigen for vaccine production as it is involved in attachment to the host cell. O.tsutsugamushi has many serotypes (Karp, Gillian, Kato and Kawazaki etc).They grow only in cell culture media Chick embryo cell culture,vero cell lines etc. They nourish on the amino acids like glutamate located in the host cell cytoplasm.The disease is transmitted by bite of chigger' the larval stage of trombiculid mite during a blood meal. Leptotrombiculid delensie is the commonest vector involved in india. The mites acquire the infection while feeding on the body fluids of rodents and field mice. The mites lives in 'mite' island which are sharply demarcated areas in the soil where the microenvironment is favourable for their survival. Especially areas cleared of forest are highly favoured. The life cycle of mite has four stages egg, larva, nymph and adult. Only the larva(chigger) feeds on humans and transmit the infection during a blood meal. The adult mite feeds on plants and hence they don't transmit the disease to humans. Normally children contact the infection while playing in mite infested areas. One study revealed that the disease was more common among individuals who defecated or urinated in the jungle or bushy areas from a squatting position.[27] Many times the bite is unnoticed due to the tiny nature of the chigger. The mites maintain the bacterial population by transovarial and transtadial transmission. [14]. The bacteria after inoculation by the chigger bite multiplies at that site producing a papule and later changing into an ulcer or eschar depending on the site. Generally the bite at warm and moist areas like groin and axilla produces an ulcer. Eschar can be produced in case if the entry site is in trunk or limbs.

Orientia tsutsugamushi infects endothelial cells preferentially though it is capable of infecting several other cells including dentritic cells, monocytes and neutrophils. The organism enters the host cell by a process called induced phagocytosis (phagocytosis in non-professional macrophages e.g. endothelial cells) with the help of host cell machinery .The bacteria does this by binding to the host extracellular matrix protein fibronectin through one of its outer membrane protein(OMP) called TSA56 .This protein is type specific and it is one of the main target for vaccine production as already mentioned.

Inside the cells they are located in phagosomes. But shortly after entering the cells orientia escapes from the phagosomes by some unknown mechanisms and enter the cytoplasm where it's nutritional requirements are met. In the cytoplasm it multiplies by binary fission and buds out from the surface of the cell spreading to the neighbouring cells.

The dissemination of the organism from here is by lymphogenous to the regional lymph nodes and haematogenous to the rest of the body. Although there are controversies regarding which is the initial cells to get infected (i.e. endothelial or dentritic cells) the recent available evidence supports that dentritic cells are infected initially[26,22].Their activation leads to elaboration of pro-inflammatory cytokines (TNF- AND IL-1).These inflammatory cytokines causes increased expression of cellular adhesion molecules by the endothelial cells through which bacteria can enter by induced phagocytosis.

Both humoral and cellular immunity are equally important in combating scrub typhus .Humoral immunity acts by inhibiting the binding of organism to host cells .Also it promotes opsanophagocytosis by professional macrophages. Cellular immunity is mainly mediated by TH1 type helper T cells through a balanced production of inflammatory cytokines[21].It has been proposed by various animal experimental studies that balanced production of the above cytokines helps in clearance of infected macrophages and overproduction may lead to complication like SIRS(29).The clinical features of scrub typhus in children are not specific and can vary from fever without focus to life threatening systemic involvement like myocarditis,meningo-encephalitis ,ARDS or renal failure[9,10,11,12]. The aim of our study is to focus on the uncomplicated forms of scrub typhus. Early diagnosis by clinical features is essential to start empirical therapy with doxycycline as delay in initiation of treatment is associated with complications and increased mortality.[16] In our study the major clinical findings are fever, toxic look, tender hepatomegaly and splenomegaly. Fever is the most common and consistent symptom. The fever is moderate to high grade . Affected children looks dull and lethargic even during the inter febrile period. This differentiates scrub typhus from malaria and simple non-specific viral illnesses. Tender hepatomegaly is seen in as much as 2/3rd of our patients. Though splenomegaly coexists with hepatomegaly isolated splenomegaly is seen in as many as 30 to 40% of our patients[4,6].This is in similarity with the previous study conducted by s.palanivel et al of india in 2010 who reported ,that 80% had hepatosplenomegaly. In almost all of these patients it is associated with elevation of ALT & AST consistent with clinical hepatitis. (ref).Vomiting is common with the onset of fever. only two patients developed a maculopapular rash sparing the palms and soles(ref).The characteristic feature of scrub typhus an eschar or ulcer which is the entry point of the organism is found in 65.38 % of our patients. Previous studies revealed that the incidence of eschar or ulcer is variable and it ranges from 7--92 %(table.1) and many times is present in the hidden sites like groin, perineum and axilla[13].Likewise many of our patients had the ulcer in the axilla and groin. The typical ulcer is around 0.5 to 1 cm with a white pustular base with tender regional lymphadenopathy[picture]. Though cough was present in 39% of the patients only three out of 26 patients(11.53%) had bilateral crepitations of the lung fields and this patients showed interstitial infiltrates in chest X.ray.

Common laboratory findings seen in our study are thrombocytopenia and elevated liver enzymes[reference].Nearly half of our patients had mild thrombocytopenia and none of them had platelet count less than 50,000/cu.mm. In an Indian study thrombocytopenia was noticed in 77% of the inpatients and that study involved critically ill patients.[10]The point inferred here is that all of our patients diagnosed as scrub typhus had mild thrombocytopenia. A few patients who had severe

thrombocytopenia tested positive for dengue also. They were not included in the study. Total leukocyte count was normal in most of our patients .[25].Scrub typhus can be confirmed by many of serological investigations and PCR. The serological investigations include weil-felix test OX-K agglutination test, indirect fluorescent antibody assay(IFA), Indirect immunoperoxidase assay(IIPA).Apart from these some rapid diagnostic tests are also available. In developing countries like India the problem don't lies in choosing the test based on sensitivity and specificity but based on availability and cost of the investigations. Although IFA is considered the reference test with a sensitivity of around 90% it is not widely available. Also we don't have baseline titre in a particular group of population for the interpretation of IFA. However Weil-felix test which is considered to be less sensitive is still useful in our country when combined with clinical presentation and disease endemicity. [23]. In our study 20 of the 26 patients showed a positive result with weil-felix test.

Scrub typhus dramatically responds to doxycycline and the fever subsides within a day or two after starting the drug[6,18].All of our patients responded to doxycycline and 75% responded within 24 hrs. Azithromycin is also equally efficacious[19]. Doxycycline can be safely used even in children less than 8yrs of age, as teeth discolouration is commonly seen at a higher total dose and prolonged therapy.[20]

To conclude scrub typhus is not uncommon in children and it should top the list of differential diagnosis in evaluating a febrile child. So it is prudent to start the child of undiagnosed fever of more than a week on empirical doxycycline as it may not be always possible to confirm the diagnosis by laboratory means. Further the case fatality is very high with late initiation of therapy.[16].Also most of the published studies we see in literature are of scrub typhus with associated complications(ARDS, renal failure, SIRS, shock).But the thing is scrub typhus need not be always a complicated one or an inpatient diagnosis. It can be very well picked up in the outpatient department itself and that even by simple means like thorough clinical examination[13], searching for an ulcer or eschar and no sophisticated investigations are required which are very far away for paediatricians in and around the rural areas of India.

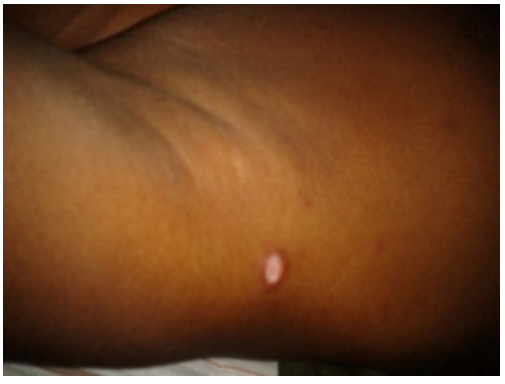

Figure 2 ,An eschar over the scrotum

	Type of study	No of patients	Fever	Eschar	Lymphadenopathy	Hepatomegaly	splenomegaly	Cough	Rash
eastern Taiwan, 2000-2005	retrospective	28	100	50	42.9	35.7		50	35.7
China study 93-2004	Retrospective	56	100	96	86				98
Descriptive study, india,2010-2011	Descriptive	67	100	46	--	80	80	73	35
Northern china 1995-2006	retrospective	70	100	84	61	56	56	---	91
North eastern india,oct 2009-10	retrospective	24	100	41.7	12.5	33.3	45.8	37.5	--
Trans R Soc Trop Med Hyg. 2004; 98(6):354-9	retrospective	73	--	7		59	18	22	7

Lab Parameter		Number	Percentage
Hb(<11.5gms)		11	42.30%
TLC(cu.mm)	<4000	4	15.38%
	>11000	3	11.53%
Platelet(cu.mm)	1.5L—1L	13	50%
	1L—50000	2	7.69%
	<50000	0	--
ALT(>40)		20	76.92%
AST(>40)		20	76.92%
S.Albumin(<3.5gms)		13	50%
Albuminuria(trace & above)		20	76.92%

The patient treated with doxycycline was afebrile with in 18 hours of drug therapy whereas those treated with azithromycin required minimum 48 hours for defervescence.

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