

Original Article

Clinical Vignettes of Scrub Typhus Meningitis

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Aim : Scrub Typhus with neurological manifestations are often described. We present here series of five cases of neurological manifestations in the form of meningitis in patients with Scrub Typhus.

Background : Scrub Typhus is an endemic disease in India caused by *Orientia tsutsugamushi*, transmitted by trombiculid mites. It is an important cause of acute febrile illness in India. Signs & symptoms include fever, headache, myalgia & GI symptoms & is generally associated with morbilliform rash (<40%), eschar (<50%) which is due to bite of the mite. Abnormal LFTs & lymphocytosis are commonly seen in early phase of illness. It's often labelled as Pyrexia of Unknown Origin (PUO). Early diagnosis & prompt administration of therapy mostly leads to complete recovery.

Method : We screened patients presenting with fever, headache, neck stiffness, vomiting, photophobia and evaluated them for meningitis. Patients in whom no cause of fever could be established, having lymphocytosis, hyponatremia & transaminitis, they were tested for Scrub Typhus by using Indirect immunofluorescence & detection of IgM antibody.

Conclusion : This study will help clinicians to have a stronger suspicion of Scrub Typhus in undiagnosed febrile patients.

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Key words : Scrub Typhus, Rickettsia, Eschar, Hyponatremia, Meningitis.

Last summer (ie, 1877), I had the opportunity of observing a disease which, so far as I know, is peculiar to Japan and has not yet been, described. It occurs, moreover, in certain well-marked districts and at a particular season of the year, so that the opportunities of investigating it do not often occur. It is known here as the Shima-mushi, or Island-insect Disease and is so-named from the belief that it is caused by the bite or sting of some insect peculiar to certain islands in the river known as Shinagawa, which empties itself into the sea at Niigata.
— **Theobald Adrian Palm**

To the Western World, first reported incident of Scrub Typhus was noted by a physician named Theodore Adrian Palm in the year of 1878, which was prevalent on the banks of Shinano River. However, a Japanese physician named Hakuju Hashimoto gave the medical description of the disease from Niigata prefecture in the year of 1808. The earliest record of the disease came from 3rd Century China. Name of the disease came from “tsutsuga” (fever, illness) and “mushi” (bug, insect). During the second world war in the Pacific theatre the disease become very prevalent and both the Allied and Japanese forces suffered a huge blow from Scrub Typhus and has even outnumbered weapon related casualties.

Scrub Typhus is an acute febrile illness caused by *Orientia tsutsugamushi* and is characterized by an

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Editor's Comment :

- Though Scrub typhus is commonly encountered in patients either residing in hilly or forest areas or having a travel history to endemic areas, due to urbanisation and afforestation it is frequently found in urban areas nowadays. Rickettsial cause still remains an important differential diagnosis for patients presenting with meningitis testing negative for the commonly encountered causes.

eschar, lymphadenopathy, multisystem involvement and a rapid response to doxycycline. Scrub Typhus is seen in to the so-called Tsutsugamushi Triangle, a region covering the Russian Far East in the North, Japan in the East, Northern Australia in the South and Afghanistan in the West and is related mostly to agricultural activities¹. In our institute based on Southern Fringes of Kolkata receiving patients from both 24-Parganas which has primarily a rural background there has been an increased identification of Scrub Typhus as a cause of fever in ward. Some of these patients landed up with complications of meningitis and meningoencephalitis. We created a profile of 21 such patients of Scrub meningitis in our institute with their varied presenting feature, clinical course and lab parameters (Table 1, Fig 1).

Investigations revealed predominant peripheral lymphocytosis, hyponatremia, raised hepatic transaminases, raised acute phase reactants (Ferritin, LDH) (Table 2).

The patients were initially given Injection Ceftriaxone and Mannitol initially (Fig 2).

All infective profile (Malaria, Dengue, Typhoid) & Viral serology were negative.

On Lumbar puncture the opening pressures were high & Cerebrospinal Fluid (CSF) findings were noted (Table 3).

MR Venogram of few patients revealed cerebral

Table 1 — Examination Findings

Patient No.	Sex	Age (Years)	Fever For Days	Eschar	Head-ache	Nuchal Rigidity	Myalgia	Altered Sensorium	Nausea/vomiting	Pulse rate	Hospital Stay (days)
1	Male	32	7	Yes	Yes	Yes	No	Yes	Yes	Bradycardia	8
2	Female	32	6	Yes	Yes	Yes	No	No	No	Bradycardia	10
3	Female	48	4	Yes	Yes	Yes	No	No	Yes	Tachycardia	7
4	Male	65	8	No	Yes	Yes	Yes	No	Yes	Bradycardia	12
5	Female	53	7	No	Yes	Yes	Yes	Yes	Yes	Tachycardia	8
6	Male	34	6	No	Yes	Yes	Yes	No	Yes	Tachycardia	9
7	Female	42	4	Yes	Yes	Yes	Yes	No	Yes	Tachycardia	9
8	Male	58	3	Yes	Yes	Yes	Yes	Yes	Yes	Tachycardia	7
9	Female	52	7	Yes	Yes	Yes	Yes	No	Yes	Tachycardia	6
10	Female	64	4	Yes	Yes	Yes	Yes	Yes	Yes	Tachycardia	12
11	Male	32	5	Yes	Yes	Yes	Yes	No	Yes	Tachycardia	10
12	Male	22	4	Yes	Yes	Yes	Yes	No	No	Tachycardia	9
13	Female	56	4	Yes	Yes	Yes	No	Yes	No	Tachycardia	8
14	Female	44	7	No	Yes	Yes	No	Yes	No	Bradycardia	7
15	Male	29	7	Yes	Yes	Yes	Yes	No	No	Tachycardia	11
16	Male	18	4	No	Yes	Yes	No	Yes	No	Tachycardia	8
17	Female	35	6	No	Yes	Yes	Yes	Yes	No	Tachycardia	8
18	Female	43	5	No	Yes	Yes	No	No	No	Bradycardia	7
19	Male	51	6	Yes	Yes	Yes	No	Yes	Yes	Bradycardia	6
20	Female	58	7	No	Yes	Yes	Yes	No	Yes	Tachycardia	6
21	Female	27	7	No	Yes	Yes	No	No	No	Tachycardia	8

venous sinus thrombosis (involving Superior sagittal sinus, Straight sinus, right transverse sinus) (Fig 3).

Scrub typhus IgM (IFA method) were positive in all cases (Fig 4).

Hence, the patients were diagnosed to be of Scrub Typhus Meningitis.

They responded well to Doxycycline (100 mg q12h for 10-15 days). Sensorium improved within 2-3 days of starting therapy. Out of the 21 cases there were only 2 deaths reported.

MATERIALS AND METHODS

Type of study : Cross sectional study

Study setting : KPC

Medical College & Hospital, Jadavpur, Kolkata-700032

Place of study : Admitted patients in the Department of General Medicine, Intensive care unit in KPC Medical College & Hospital

Period of study : 8 months (May to December 2019)

Study population: Patients presenting with fever for more than a week.

Sample size : Out of all the patients being



Fig 1 — Eschars

Table 2 — Investigation Findings

Patient no	Hb Gm%	TLC Mil/cumm	PLC Lac/cumm	CRP mg/L	BIL mg/dl	AST U/L	ALT U/L	ALP U/L	ALB Gm/dl	CPK U/L	LDH U/L	Cr mg/dl	Urea mg/dl	Na+ mEq/L	K+ mEq/L
1	13.5	10700	1.10	24	0.8	77	68	406	3.6	650	1060	0.9	28	136	3.9
2	10.2	10200	0.87	48	2.1	87	68	187	3.2	700	887	1.2	44	131	3.4
3	11.6	8600	1.64	36	1.5	66	78	276	3.4	466	654	1.1	36	130	3.2
4	8.9	9800	1.26	24	1.2	66	89	238	3.0	864	746	1.2	48	128	3.2
5	12	12000	1.34	12	1.8	84	76	268	3.2	586	688	1.3	50	126	3.6
6	14	12600	1.38	24	1.4	64	78	300	3.0	458	564	1.4	48	131	3.7
7	12.2	8600	1.30	12	1.6	56	68	238	3.4	606	568	1.2	28	134	3.8
8	10.4	9800	1.10	48	1.2	64	78	342	3.0	678	688	0.9	32	130	3.8
9	9.2	12500	1.35	36	1.8	78	88	238	3.4	876	1060	1.2	34	138	4.0
10	10.6	8800	1.80	48	2.2	84	76	286	3.2	986	866	1.4	44	132	4.0
11	13.2	14000	1.4	64	2.4	78	88	284	3.4	678	776	0.8	32	126	3.8
12	14.4	11300	1.54	24	1.6	66	68	248	3.2	566	709	0.9	26	134	4.0
13	12.6	14300	1.27	48	2.4	67	86	308	2.8	877	823	0.8	34	136	3.8
14	11.2	12700	1.68	24	2.2	86	82	243	3.8	457	569	0.9	32	134	3.9
15	12.5	8750	1.90	12	1.4	76	78	268	3.6	866	788	1.2	34	138	3.8
16	11.8	9800	1.87	12	1.5	77	87	246	3.8	477	677	1.3	44	132	3.9
17	9.7	8800	1.65	12	1.4	76	86	286	3.4	662	568	1.2	32	130	3.6
18	8.4	7800	1.67	06	1.2	64	64	286	3.2	544	466	1.2	28	132	3.8
19	13.8	11400	1.38	12	1.7	46	54	179	3.2	566	658	1.3	36	134	3.4
20	10.8	12340	1.46	06	1.2	39	48	178	3.6	499	567	1.2	33	139	3.8
21	11.2	10400	1.65	12	1.4	68	56	188	4.0	563	876	1.3	34	135	4.2

NCCT Brain revealed diffuse cerebral oedema with effaced ventricles.

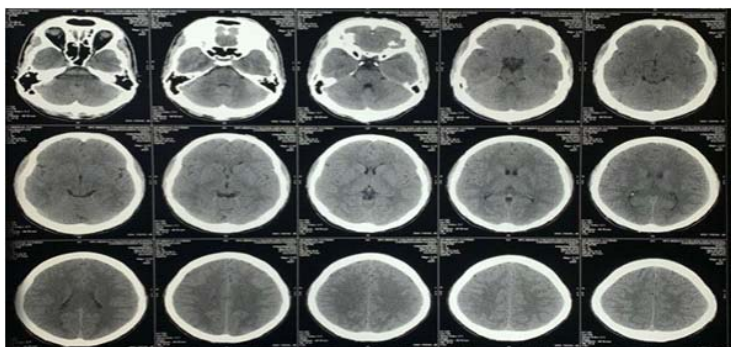


Fig 2 — NCCT Finding

<0.05 were considered statistically significant.

DISCUSSION

Scrub Typhus is acute febrile illness, caused by *Orientia tsutsugamushi* and is transmitted to humans by trombiculid mites. It is commonly seen during monsoon and post monsoon season in our country², causing lot of morbidities and occasional mortality. It involves all organ system of body³ commonly characterised by fever, rash, lymphadenopathy, myocarditis and pneumonitis. The most characteristic skin manifestation is *Eschar* which is seen in about 4%-46% in Indian population⁴. Neurological involvement, both Peripheral and Central Nervous System are well known⁵. Most common Central Nervous System (CNS) manifestation is Meningitis and Meningo-encephalitis; also seen are Cerebral Infarction, Cerebral Venous Sinus Thrombosis Acute Disseminated Encephalomyelitis (ADEM) and cranial neuropathies (mostly isolated)⁶.

It has varied presentation & is an important cause of morbidity & mortality. Common laboratory findings were normal or low WBC counts with predominant lymphocytosis, mild to moderate serum elevations of hepatic enzymes and hyponatremia. Hyponatremia is an important finding⁷ and was almost invariably found in all patients with Scrub Typhus.

After its re-emergence, Scrub Typhus has become an important cause of morbidity and mortality in patients presenting with febrile illness during monsoon and postmonsoon season². According to WHO, Scrub typhus is probably one of the most underdiagnosed and under-reported febrile illnesses requiring hospitalisation⁸. It is transmitted by bite of Trombiculid Mites during the season of activity or travel to or residence in an endemic geographic region during the incubation period (6-21 days)⁹. A clinician must possess high degree of suspicion for Scrub Typhus if a patient of febrile illness tests negative for all the common infective profile as per the local infection control guidelines. Though Scrub Typhus is commonly encountered in patients either residing in hilly or forest areas or having a travel history to endemic areas, due to urbanisation and afforestation it is frequently found in urban areas nowadays. Scrub Typhus was diagnosed in our patient by the presence of IgM antibody in serum. Neurological involvement in Scrub Typhus has been well documented in literature⁵. Meningitis/ meningo-encephalitis is the most common manifestation⁴ (15%-50% cases)¹⁰.

CONCLUSION

Scrub Typhus can present with variety of neurological manifestations. Scrub Typhus meningitis is a milder complication compared to Respiratory or Gastrointestinal problems even if it is associated with altered sensorium or cranial nerve deficits and generally resolves completely

Table 3 — CSF Findings

Patient No.	Sex	Age (Years)	Cell count (cells/cu.mm)	Cell type	Protein (mg/dl)	ADA (U/L)
1	Male	32	50	Mononuclear cells	21	6.0
2	Female	32	20	Mononuclear cells	140	3.0
3	Female	48	4	Lymphocytes	122	5.0
4	Male	65	10	Mononuclear cells	22.7	6.4
5	Female	53	0	Acellular	135.4	3.0
6	Male	34	10	Mononuclear cells	22	4.0
7	Female	42	3	Lymphocytes	130	6.0
8	Male	58	2	Mononuclear cells	120	8.0
9	Female	52	0	Acellular	27	5.0
10	Female	64	0	Acellular	116	2.0
11	Male	32	22	Mononuclear cells	78	5.0
12	Male	22	10	Mononuclear cells	32	4.0
13	Female	56	5	Lymphocytes	122	8.0
14	Female	44	7	Mononuclear cells	44	6.0
15	Male	29	12	Mononuclear cells	60	4.0
16	Male	18	10	Mononuclear cells	51	5.0
17	Female	35	4	Lymphocytes	26	3.0
18	Female	43	2	Lymphocytes	140	10.0
19	Male	51	20	Mononuclear cells	84	2.0
20	Female	58	0	Acellular	124	3.0
21	Female	27	0	Acellular	132	2.0

admitted in KPCMCH with fever, during the study period, first 100 consecutive patients fulfilling the study criteria was selected for the study.

Selection criteria :

(1) Inclusion criteria —

- Patients admitted with fever but tested negative for commonly sent infective profile according to local guidelines for infectious disease (Eg: Dengue NS1 antigen, MP, MPDA, TyphidotM, viral serology).

- Patients with Pyrexia of Unknown Origin.
- Patients giving consent for the study.

(2) Exclusion criteria —

- Already diagnosed cases of fever on admission.
- Immunocompromised patients.
- Patients not giving consent for the study.

Test performed : Serologic assays, Scrub typhus IgM (Indirect Immunofluorescence Assay method) were performed for all the suspected patients.

Statistical analysis : Descriptive values were expressed as mean ± standard deviation and percentage accordingly. The *p* values were two-tailed and those

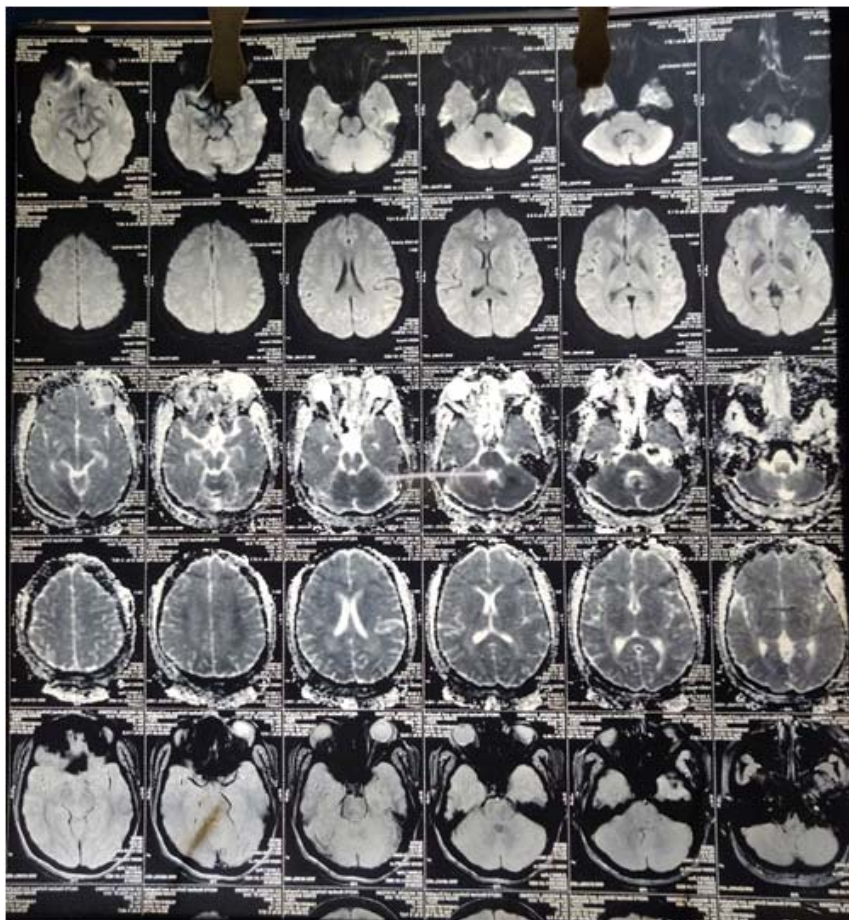


Fig 3 — MRI Brain suggested meningitis

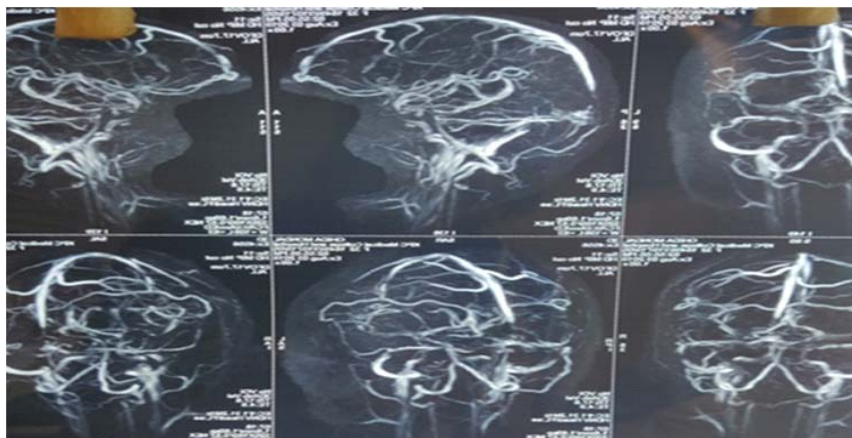


Fig 4 — MR Venogram

with Doxycycline Therapy. Due to the presence of lymphocytic pleocytosis with increased CSF protein, TBM is a close differential diagnosis. This may result in rifampicin-based ATT masking the diagnosis of Scrub Typhus and sometimes results in patients continuing long term therapy for TBM. Since India is endemic for both TB and Scrub Typhus, awareness of simple-to- treat

Scrub Typhus with access to specific tests like scrub IgM and Cerebrospinal Fluid (CSF) Adenosine Deaminase (ADA) may go a long way in avoiding unwarranted treatment in patients. Older age, longer duration of fever, thrombocytopenia, abnormal liver and renal function, hyponatremia and elevated C-Reactive Protein (CRP) levels are associated with severe complications and prolonged treatment duration. Clinically, younger patient population, rapid diagnosis, and prompt treatment may be associated with a shortened disease course and a better outcome. We should be vigilant so that proper diagnosis and management can be given in due time with satisfactory improvement.

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Conflict of interest : None

Ethical Approval : Taken

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