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TYPHOYD FEVER OF PROTRACTED COURSE

Rodolfo TEIXEIRA [1]

SUMMARY

The author reports on 16 cases of typhoid fever of long duration where the clinical course of the disease averaged nine months, ranging from six to twelve months. The cardinal features of the clinical picture presented by these patients are reviewed and laboratory findings discussed. The difficulties associated with the clinical differentiation from conditions which simulate this variety of typhoid fever are pointed out. Kala-azar is considered the disease which more often needs to be taken into account in the differential diagnosis. Problems related to the laboratory diagnosis are emphasized. A possible role of *S. mansoni* infection, which was demonstrated in all but one case, in the pathogenesis of the disease, is suggested.

INTRODUCTION

It is well-known that the incidence of mansoni schistosomiasis in Northeastern Brazil is strikingly high. Also relatively frequent in that area are diseases simulating schistosomiasis by the presence of marked spleen enlargement and often of fever among their chief clinical manifestations. Visceral leishmaniasis (Kala-azar) is an example of the latter.

We have recently reported on cases whose main clinical features were marked splenomegaly and a long-term fever, from which *Salmonella typhi* was isolated [3, 4]. As these patients were found to harbour a *S. mansoni* infection, a possible role of schistosomiasis in the determination of the unusual clinical course of typhoid fever was suggested.

Since our last report, we have had an opportunity to observe new features in connection with the study of some additional cases.

Sixteen patients from five different and wide apart municipalities in Bahia State, seen between September 1957 and May 1959, provided the material for the present communication. Among the cases, twelve came from a single town where an outbreak of typhoid fever occurred. There were six males and ten females. The age at admission ranged from five to thirty years; the average was fourteen. A complete history was elicited, a detailed physical examination performed and pertinent laboratory data were obtained from each patient. An evaluation of the clinical records of these patients is presented below.

CLINICAL PICTURE

The unusual clinical picture of typhoid fever was characterized by the following cardinal features which are listed according to the order of their relative importance and frequency in which they occurred:

a) An excessively protracted clinical course ranging from six months to one year and averaging nine months in duration.

b) Fever, irregular or recurrent in type (Fig. 1). It should be pointed out that the temperature patterns were not the same in

Fac. Med. da Univ. Bahia — Clín. Doenças Trop. e Infectuosas (Prof. A. Prata).
(1) Assistant Professor of Tropical Medicine.

the different stages of the disease. History data were retrospectively obtained which indicated that fever was continuous in character during the first month of clinical course in all cases.

most of whom exhibited a marked splenomegaly. The spleen enlargement was of moderate degree in some additional patients. The spleen decreased in size in practically every case when the patients were put on

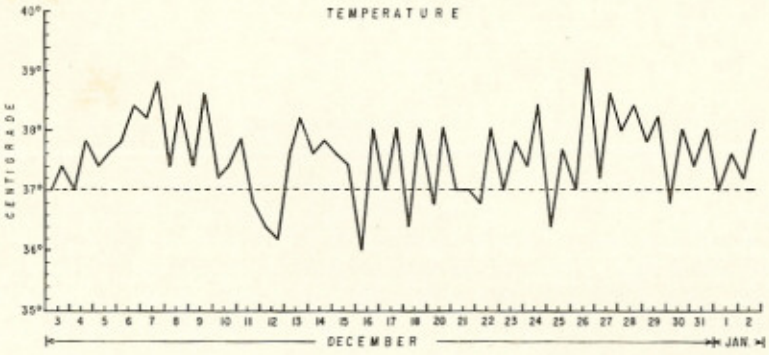

Fig. 1 — Temperature chart during first hospital month (Case No. 1).

c) Diarrhea was invariably present usually in the form of three to six daily bowel movements, unaccompanied by abdominal cramps and associated with the passage of watery stools. The diarrhea usually subsided promptly after the administration of chloramphenicol to the patients.

d) Liver enlargement was present in every case. The liver was firm and its anterior edge was regular. The hepatomegaly partly subsided on chloramphenicol therapy but some residual liver enlargement remained in practically every patient (Fig. 2).

e) Splenomegaly — The spleen was felt below the left costal margin in all patients,

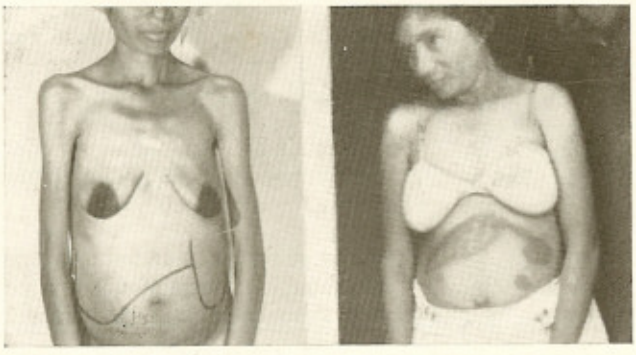

Fig. 2 — Photographs of case No. 7 before and after chloramphenicol treatment.

chloramphenicol therapy. In a few patients the splenomegaly subsided completely. In some other patients, however, a residual splenomegaly remained suggesting that, in such cases, the spleen enlargement was probably related in part to the *S. mansoni* infection.

f) Skin lesions which were observed in five patients were always localized in the lower limbs, bilaterally. They were (Fig. 3) simetrically distributed and appeared in bursts of purplish-pink macules. Sparsely distributed at first, they soon became confluent, lasting six days on the average. Their onset was coincident with that of articular pain which was most frequently localized over the knees and ankles. The skin rash subsided completely in all patients leaving no residual alterations.

g) Other manifestations such as weight loss, oedema of the lower extremities and paleness of the mucosal membranes were also observed. In one case who developed marked generalized oedema and ascitis signs of severe renal failure became apparent.

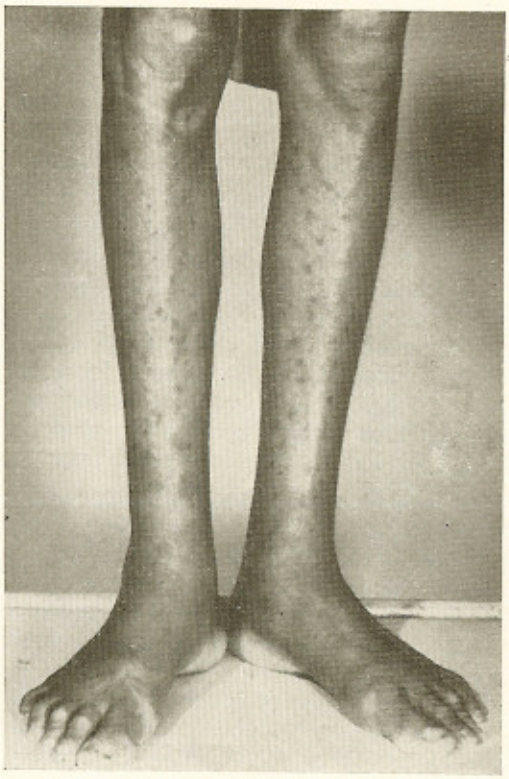

Fig. 3 — Purpuric spots scattered throughout both legs (Case No. 7).

LABORATORY FINDINGS

a) The blood picture shown by these patients depicted moderately elevated or normal white blood cell counts, absolute and relative increase in eosinophils and absolute monocytosis. Segmented neutrophils were normal or moderately increased in absolute numbers. Stippling was rarely seen. Red blood cell counts were usually low and hemoglobin content remarkably reduced. Reticulocytes were invariably increased in number.

The bone marrow was very hyperplastic, due chiefly to increase in the granulocytic series. Eosinophils and plasma cells were relatively numerous and reticulum cells reduced in number. The erythroblastic series exhibited an accelerated maturation curve.

b) Total plasma proteins were normal or slightly reduced. The globulin fraction was moderately increased and the albumin reduced. Electrophoretic fractionation of plasma proteins performed for a single case revealed an albumin fraction greatly reduced and globulin fractions markedly increased in concentration. Two fractions of gamma globulin were seen in this case, in whom, it should be pointed out, signs of severe renal failure developed.

c) Liver functions tests, particularly the flocculation reactions, were always positive.

d) Renal function tests were performed for the case exhibiting evidence of kidney injury from whom *S. typhi* was isolated from the urine. The results (P.S.P. excretion, concentration test, urinalysis, urea nitrogen and creatinin determinations) were consistent with the clinical evidence of renal damage. Urinalysis, blood urea, and creatinin determinations were obtained for some other cases. Traces of protein and, rarely, casts were seen whereas blood urea and creatinin were always within normal limits.

e) Needle biopsy of the liver revealed proliferation of Kupffer cells, fat metamor-

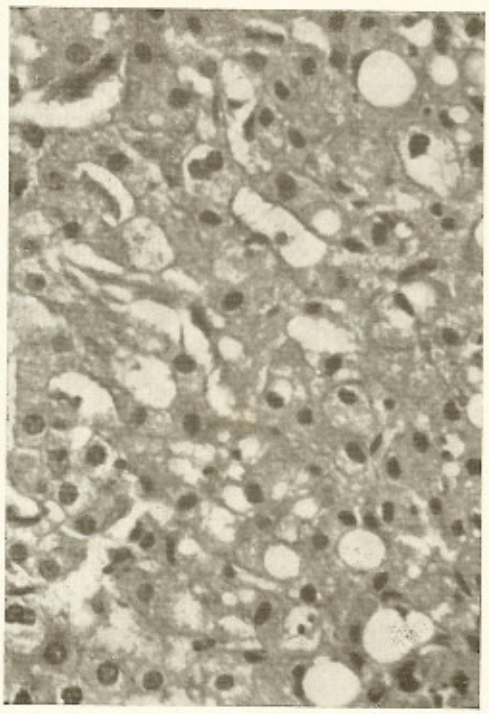

Fig. 4 — Liver biopsy. The hepatocytes show vacuolization. Küpffer cells are swollen and increased in number.

phosis and scattered neutrophilic, lymphocytic and monocytic infiltrates (Fig. 4). In one case the above alterations were observed to disappear after chloramphenicol therapy.

f) By means of skin biopsy it was shown that the purplish lesions were characterized by recent hemorrhagic areas in the superficial dermis and moderate lymphocytic infiltrate. Blood vessel lesions were not observed.

g) A single stool examination for ova of *S. mansoni* was positive in all but one patient; an infectivity rate of 92.3%. A skin test with adult worm antigen yielded a positive result in four out of eight patients (50%), a doubtfully positive in one and a slightly positive result in another patient.

DIAGNOSIS

An essential requirement for the diagnosis of chronic typhoid fever is the awareness on the part of the clinician dealing with a case whose main manifestations are a long-term fever, hepatomegaly, diarrhea and weight loss.

Kala-azar is, undoubtedly, the disease which more frequently simulates the clinical picture described above. The differential diagnosis between chronic typhoid fever and kala-azar may be extremely difficult to be made. Diarrhea, which is much more frequent in chronic typhoid fever than in kala-azar, is of particular value in that connection. Epistaxis, on the other hand, which is a common sign in kala-azar, was present in one single case of the present series. By further clinical data, kala-azar and chronic typhoid fever may be otherwise undistinguishable.

One should also bear in mind the fact that other diseases like salmonellosis (particularly those due to *S. paratyphi* A and B and to *S. panama* infections), malaria, histoplasmosis, brucellosis, chronic meningococcal septicaemia and leukosis, should be properly distinguished from chronic typhoid fever.

The laboratory is of paramount importance in the diagnosis. The demonstration of *S. typhi* in the blood or stools as well as a positive Widal agglutination test are decisive findings. It should be pointed out that blood cultures have usually to be obtained several times before one gets a positive result. Nevertheless, our experience is based on methods which are known to give a relatively low yield of positivity as it is the case when blood cultures are grown in plain bile broth. It is possible that, if more sensitive methods were used, and cultures from bone marrow and from streptokinase treated blood clots obtained [4], the positivity rate would be increased (Table I).

TABLE I

Results of Widal Agglutination Test and blood, stool and urine cultures.

Case No.	*Widal agglutination test (reciprocal of titers)*			*Blood culture*	*Stool culture*	*Urine culture*
	Agg. O	*Agg. H*	*Agg. Vi*			
1	400	800	—	—	+	...
2	—	400	—	—	—	...
3	—	400	—	—	—	...
4	600	600	—	—	—	...
5	—	400	—	—	—	...
6	—	600	—	—	—	...
7	—	400	—	+	+	—
8	—	600	300	—	—	—
9	—	600	200	+	+	—
10	100	600	—	—	—	—
11	—	200	—	—	—	...
12	—	200	—	—	—	...
13	...	...	...	+	+	...
14	...	...	...	...	+	...
15	200	200	...	+	+	...
16	—	400	—	+	—	+

In one case three blood cultures of samples taken at different hours of a single day yielded two positive and one negative result.

With stool cultures results were better than those obtained with blood cultures; a higher positivity rate was attained.

Results of the Widal agglutination test could not be interpreted in these cases the way they are interpreted in typical cases of typhoid fever. Firstly, agglutinin titers were in general very low if agglutination was not entirely absent as it occurred in two patients from whom *S. typhi* was recovered from blood or stool cultures. Secondly, the H agglutinin was present more often and at higher titers than the 0 agglutinin. Among our sixteen cases, H agglutinin alone was found in eight patients, three of whom had positive blood cultures. Both H and Vi agglutinins were present in two cases and in two additional cases, as already mentioned, the Widal agglutination test was entirely negative.

As an attempt to explain these findings we suggested that, due to the prolonged course of infection, the titers of 0 agglutinin had been markedly reduced and agglutination eventually disappeared [4]. A well established fact is that the ability of sera to agglutinate the somatic 0 antigen develops early in the course of typhoid infection to last a relatively short period of time. We ventured, moreover, a hypothesis that our patients had actually a modified immunologic response to *S. typhi* infection.

TREATMENT

Chloramphenicol was the drug employed in the treatment of all sixteen cases. Each patient was given a daily dose of 50 mg of the drug per kilogram of body weight and that dose was maintained at least for 72 hours after temperature had become normal. In addition, two doses of a typhoid vaccine at a seven-day interval were administered to each patient.

It should be emphasized that the patient's responses to chloramphenicol therapy were very prompt; fall in temperature to normal levels occurred within 24 hours after therapy was started. The other signs also subsided very rapidly. The anemia, for instance, which had been observed in some cases to be very resistant to iron, protein and blood transfusion therapies, improved considerably on specific therapy. No side effects of chloramphenicol therapy were observed. Relapse occurred in a single case requiring a second series of chloramphenicol.

DISCUSSION

We have attempeted in a previous paper to explain the pathogenesis of chronic typhoid fever and discussed the possible roles of agent and host factors in its determination [4]. We then suggested the need for a careful typing of the strain of *S. typhi* isolated from our cases. The fact that the first patients had come from a single place and had become sick within a short period of time seemed to indicate that we were possibly dealing with a bacterial strain whose behaviour was very unusual. However, as four additional cases studied later had come from different and far-apart geographical locations in addition to the fact that there was no apparent interrelationship between dates of the onset of illness in these patients, appeared to render the hypothesis of a new bacterial strain very unlikely. On the other hand, since schistosomiasis had been demonstrated by means of a single stool examination in all but one patient, we became impressed by the frequency of the association between these disease entities. It should be mentioned that a possible association between *S. mansoni* infection and typhoid fever was just suggested by FERREIRA [1] and between the latter and *S. japonicum* infection by TAI TZE-YING [2]. A reasonable hypothesis seems to be that mansoni schistosomiasis would modify the R.E.S. in such a way so as to decrease its ability to react against *S. typhi* infection. If this hypothesis is correct, one should wonder as to whether or not schistosomiasis could also modify the course of

TEIXEIRA, R. — Typhoid fever of protracted course. Rev. Inst. Med. trop. São Paulo 2:65-70, 1960.

diseases due to other bacterial infections, particularly those caused by bacteria whose behaviour is similar to that of *S. typhi.*

RESUMO

Forma prolongada de febre tifóide.

O autor estuda 16 casos de febre tifóide, de longa duração, nos quais o curso clínico da doença durou em média 9 meses, variando entre os extremos de 6 e 12 meses.

O quadro clínico compreendia: febre, de tipo irregular ou recorrente; diarréia; hepatomegalia e esplenomegalia; em alguns casos, manifestações cutâneas (máculas róseo-violáceas) nos membros inferiores, além de outras manifestações eventuais.

O laboratório revelou, nesses pacientes, leucocitose com eosinofilia; anemia e reticulocitose; hiperplasia da medula, devida principalmente à série granulocítica; curva de maturação acelerada para a série eritroblástica. Provas de função hepática sempre positivas. O exame de fezes foi positivo para *Schistosoma mansoni* em todos menos um caso.

Os problemas ligados ao diagnóstico diferencial com outras condições mórbidas semelhantes, particularmente o calazar, e ao diagnóstico laboratorial são discutidos. Sugere-se que a infestação esquistossomótica possa ter um papel na patogenia desta forma da doença.

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