Relapsing Typhoid Fever: Report of a Case with Immunological Studies*

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SUMMARY **A 14-year-old girl had relapsing typhoid fever for more than 3 months despite optimum and appropriate antibiotic therapy. A defective functioning of phagocytes, decreased ratio of OKT_4^+ T-lymphocyte to OKT_8^+ T-lymphocyte and negative cell-mediated immune response to *S. typhi* probably accounted for the pattern of infection seen in this patient. Long-term therapy with a high dose of an appropriate antibiotic is recommended for such a patient.**

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Patients with typhoid fever usually recover within 2 weeks after therapy of an optimum dose of appropriate antibiotic. The relapse rate of typhoid fever has been found to be 8.8 percent.[1] Eleven cases of second attacks of typhoid fever in previously healthy men,[2] and two cases of recurrent *Salmonella* infection, one in a carrier of chronic granulomatous disease,[3] and one in an immuno-compromised host,[4] have been reported in the literature. The mechanism of recurrent or relapsing *Salmonella* infection, including typhoid fever, remains unclear, or inadequate immunological studies have been reported. Some investigators have suggested that hosts who have defects in phagocyte function could have recurrent *Salmonella* infection since *Salmonella* is facultatively intracellular organism.[5]

We wish to report a case of relapsing typhoid fever in a previously healthy girl. Immunological studies revealed abnormal intracellular killing activity in phagocytes and impaired cell-mediated immunity in spite of normal antibody responses, which could, in part, explain the mechanism of relapse or recurrence of this disease.

CASE REPORT

A 14-year-old girl, previously in good health, was admitted to the hospital in March 1982 because of a high and persistent fever lasting 7 days. Haemoculture on the first day of admission was positive for *S. typhi* which was sensitive to chloramphenicol, co-trimoxazole and ampicillin. When typhoid fever was diagnosed, the patient was given 2 grams of chloramphenicol per day orally for 8 days. Because the fever persisted, the antibiotic therapy was changed to 4 tablets of co-trimoxazole per day orally (Trimethoprim 80 mg and Sulfamethoxasole 400 mg per tablet) for 10 days. Her fever declined slightly. When she insisted on returning home, another 10-day course of co-trimoxazole was added.

She was readmitted to the hospital with a high fever in May 1982. Haemoculture again revealed *S. typhi* with the same antibiotic susceptibility pattern as before. The patient was started on 2 grams of chloramphenicol per day orally for 14 days. Becoming afebrile to-

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gether with improvement in her general sense of well-being, she was discharged from the hospital on an oral co-trimoxazole treatment for 14 days.

Her third admission was in June 1982, with the same pattern of fever and bacteraemia. Her condition responded dramatically to oral co-trimoxazole treatment. After her discharge from the hospital, there was no recurrence of symptoms over a two-year period of follow-up.

During the course of her hospitalisations and recovery, routine white blood-cell counts and the following immunological studies were carried out.

The nitroblue tetrazolium dye (NBT) reduction test for the intracellular killing activity of phagocytes,[6] was performed. The non-specific lymphocyte response to stimulation with mitogen phytohaemagglutinin (PHA) *in vitro* was measured by blast transformation and tritiated thymidine uptake.[7] Total T-lymphocyte (OKT_3^+), helper/inducer/suppressor T-lymphocyte (OKT_4^+) and suppressor/cytotoxic T-lymphocyte (OKT_8^+), were estimated by using an indirect immunofluorescent technique with monoclonal antibodies (Ortho Pharmaceutical, Raritan, NJ). The leukocytes migration inhibition test (LMIT) for the specific cell-mediated immune response[8] was done using protein extraction (Barber protein, BP) and lipopolysaccharide (LPS) of *S. typhi* as antigens, with Barber's[9] and Neoh's[10] methods of extraction, respectively. The specific antibody response to *S. typhi* was measured by the standard Widal test using antigen suspensions purchased from Gamma Diagnostic (Div. Gamma Biologicals, Houston, Texas).

The results (Table 1) show a defect in the intracellular killing activity of phagocytes during the girl's illness and recovery in the NBT reduction test. Her PHA stimulation tests were normal. The percentages of OKT_3^+ T-lymphocyte (total T-lymphocyte) were normal. The ratios of OKT_4^+ (helper/inducer/suppressor) to OKT_8^+ (suppressor/cytotoxic) T-lymphocytes all decreased except for one study during early recovery (Aug, 1982). The LMIT showed no specific cell-mediated immune response (MI>0.8) to either antigen of *S. typhi* during her illness and recovery except for one study in early recovery (Aug, 1982). The Widal test showed high anti-H and anti-O titres during her illness and a few months after recovery, and declined to low barely detectable levels later.

Her total white-blood cell counts were low during illness, but otherwise normal. The percentages of neutrophils and lymphocytes were comparable in all studies. These results indicated no correlation between low total white-blood cell count and abnormal immunological findings in the patient.

DISCUSSION

Typhoid fever is caused by ingestion of *Salmonella typhi*. When

Table 1 Results of immunological studies, total white blood cells and differential counts during the course of the patient's illness and recovery.

	% NBT	% PHA	% OKT				MI of LMIT		Reciprocal antibody titre		WBC	% Differential count			
			T3/L	T4/T3	T8/T3	T4:T8	BP	LPS	H	O	per mm^3	N	L	M	E
Apr. 82 (1st admission)	–	–	–	–	–	–	0.83	1.06	400	80	3,500	54	42	4	0
June 82 (3rd admission)	R = 0 S = 3	71	86.0	22.3	31.7	0.70	0.91	0.94	3,200	160	3,300	52	43	5	0
Aug. 82 (recovery)	–	–	76.9	57.2	37.9	1.50	0.59	0.78	1,600	160	5,900	47	49	4	0
Sept. 82 (recovery)	R = 8 S = 7	73	79.6	39.1	51.1	0.76	0.91	0.89	1,600	160	6,500	50	46	2	2
Nov. 82 (recovery)	–	–	80.3	35.5	51.9	0.68	0.78	1.03	200	160	5,750	81	18	0	1
June 83 (recovery)	–	–	80.5	41.9	39.7	1.06	0.91	0.93	200	80	7,750	75	20	3	2
Aug. 83 (recovery)	–	–	76.5	45.0	54.2	0.83	0.90	0.90	400	80	6,300	56	40	2	2
Nov. 83 (recovery)	R = 1 S = 2	88	–	–	–	–	–	–	–	–	6,500	54	43	1	2
Normal control	R < 10 S > 50	60-90	72.0± 1.39	55.7± 1.18	40.8± 1.06	1.45± 0.08	< 0.8	< 0.8	> 200	> 80	5,000-10,000	38-70	21-49	2.5-10.5	0-7

NBT : R = resting, S = stimulated by endotoxin
MI = migration index, < 0.8 = positive reaction
Anti-H > 200 = positive reaction; Anti-O > 80 = positive reaction

OKT : T3 = peripheral T-lymphocytes
T4 = helper/inducer/suppressor T-lymphocytes
T8 = suppressor/cytotoxic T-lymphocytes
normal valnes are presented as Mean ± SE

this organism reaches the small intestine, it can multiply and at the same time react with specific secretory IgA. If the organisms can overcome this local immune defense, they will penetrate the intestinal mucosa, reach the systemic circulation via the lymphatic system and become distributed to the organs containing tissue macrophages, i.e., liver, spleen etc. In the circulation and organs, *S. typhi* will be trapped and killed by phagocytic cells which consist of neutrophils and monocytes/macrophages. Some of these organisms can survive and multiply in phagocytes since post-phagocytic oxidative metabolism within the phagocytes, which is one of the bacteriodical processes, is diminished during this infection.[11,12] Without an appropriate antibiotic, these intracellular bacteria can be killed only by activated macrophages with the aid of immune T-lymphocytes,[13] hence the cell-mediated immunity is responsible for the recovery of the disease.[14] The specific antibodies in the circulation are produced in response to *Salmonella.* The function of these is to help the uptake of the pathogens during the early phase of infection while the organisms are outside phagocytes for a short time in the circulation.[15]

The mechanism of relapsing typhoid fever is unclear; however, a possible explanation should include the abnormality of either phagocytes or T-lymphocytes or both. In the present case, an abnormal intracellular killing activity of the patient's phagocytes has been revealed by the NBT reduction test. NBT, being a non-specific test, becomes positive in any bacterial infection and bacteraemia.[16] Usually the level of NBT positive cells is very high in pyogenic infection, but lower in typhoid disease.[17] Lenney *et al*[16] found that an overwhelming bacterial infection may cause a false-negative test. This is not the explanation of the present case because the negative results during her complete recovery proved that the real defect was in her phagocytes. Her PHA stimulation tests were normal, which indicates normal lymphocyte proliferation in response to antigens in general, since this patient never had such problems with other infections.

She had a reduced ratio of OKT_4^+ (helper/inducer/suppressor) to OKT_8^+ (suppressor/cytotoxic) T-lymphocyte with negative LMIT during her illness and recovery, except during early recovery, which suggests that the defect was also in her lymphocyte subpopulations. A low level of helper T-lymphocytes or a high level of suppressor T-lymphocytes might have been responsible for her unresponsiveness to both antigens of *S. typhi* in LMIT. Her abnormal T-lymphocyte subpopulations returned to normal and specific function became responsive during her early recovery. There is no good explanation for this transient immunological recovery, but this finding goes along with her clinical improvement.

High anti-H and anti-O titres on the 3rd admission support the idea that specific circulatory antibodies do not play an important role in recovery.[14,18-20] There was also no correlation between Widal agglutination titre and LMIT positivity, which indicates that these are independent of each other and require different populations of helper T-lymphocytes.

The above immunological data suggest the important role of phagocytes and an appropriate proportion of T-lymphocyte subpopulations for recovery from typhoid fever. We feel that the host who has defective phagocyte functioning with or without low ratio of OKT_4^+ to OKT_8^+ T-lymphocytes will possibly have recurrent or relapse disease. Prolonged and high doses of appropriate antibiotic should therefore be considered. The finding also suggests that further investigations of the role of these cells in the pathogenesis of this disease should be made.

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