Am. J. Trop. Med. Hyg., 36(2), 1987, pp. 315–320

TOXOPLASMA ANTIBODIES AND RETINOCHOROIDITIS IN THE MARSHALL ISLANDS AND THEIR ASSOCIATION WITH EXPOSURE TO RADIOACTIVE FALLOUT

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Abstract. Nearly universal serologic evidence of *Toxoplasma gondii* infection was found to have occurred by adulthood in 517 Marshallese tested in 1981–1982. The prevalence and incidence of retinal lesions compatible with toxoplasmosis were 3.9% and 273 cases/year/100,000 seropositive persons, respectively, thus indicating a significant public health problem. Seronegativity was significantly more common in a subgroup of Marshallese that had received 110–190 rads of total-body gamma radiation as a consequence of accidental exposure to radioactive fallout in 1954. Despite this finding there was no evidence of an increase in clinically significant lesions in exposed persons.

Human infection by the ubiquitous intracellular protozoan, *Toxoplasma gondii*, is manifested by a variety of clinical syndromes, the most common being retinochoroiditis.[1] Serious illness occurs more frequently in immunosuppressed persons.[2] Despite the importance of the subject, no data describing the incidence of *Toxoplasma* retinochoroiditis are available, and even prevalence data from unselected populations are scanty. A prevalence of 0.6% was reported for a small Maryland community.[3]

The Medical Department of Brookhaven National Laboratory monitors medical care to a population of Marshallese which was accidentally exposed to radioactive fallout from a thermonuclear test detonation on Bikini atoll in 1954.[4] Tropical Pacific populations are known to have a high prevalence of positive serologic tests for *T. gondii*.[5–7] To determine if radiation exposure may have produced longterm immunosuppression which might place the exposed population at greater risk for clinical illness due to toxoplasmosis, a serologic survey for evidence of past infection, supported by ophthalmologic examinations, was undertaken. Toxoplasmosis has been described as a relatively unimportant public health problem on certain Pacific islands, in part because the high prevalence of positive serologic tests at an early age was felt to indicate that little opportunity existed for fetal infection.[6] To determine whether or not toxoplasmosis should be viewed as a serious public health threat in the Republic of the Marshall Islands, a second goal of the investigation was to evaluate the prevalence of *Toxoplasma* seropositivity and the prevalence and incidence of suspected *Toxoplasma* retinochoroiditis in a larger population of Marshallese which included unexposed individuals.

MATERIALS AND METHODS

The Republic of the Marshall Islands is located in eastern Micronesia approximately 2,500 miles southwest of Hawaii. Its population of 33,000 is spread over 29 atolls and 5 mountain-top islands. Following World War II, the Marshall Islands were made a United Nations Trust Territory under U.S. trusteeship. Two atolls, Bikini and Enewetok, were subsequently used by the U.S. government as nuclear weapons proving grounds after relocation of the island inhabitants. In 1954 radioactive fallout from a U.S. thermonuclear test on Bikini atoll descended accidentally on the populations of Rongelap and Utirik atolls located approximately 100 and 300 miles distant, respectively.[4] Eighty-six Rongelap individuals (including 4 in utero) and 159 persons on Utirik (including 8 in utero) received an estimated 110–190 and 11 rads of total-body gamma radiation, respectively. Thyroid-ab-

Accepted 9 September 1986.

FIGURE 1. Retinal lesion characteristic of toxoplasmosis which was identified in a Marshallese subject with serum antibody to *Toxoplasma gondii*.

sorbed radiation from radioiodines was much greater and has been described elsewhere.[8]

Since 1954 annual medical examinations and treatment have been offered to the exposed persons. This program has been carried out by the Medical Department of Brookhaven National Laboratory under contract to the Atomic Energy Commission (now the U.S. Department of Energy). In order to detect unsuspected medical consequences of the Rongelap and Utirik radiation exposure, an unexposed population of Marshallese has also been examined annually. That population, termed the "comparison" group, is statistically similar to both of the exposed populations in age and sex distribution.[9] In addition, other Marshallese are included in the examinations on the basis of humanitarian need as resources permit. Almost all persons examined resided on one of four islands: the remote islands of Rongelap and Utirik, where fallout had settled, and Ebeye and Majuro, the Marshallese population centers.

During the 1981 examinations, retinal lesions compatible with toxoplasmosis were observed using indirect and direct ophthalmoscopy performed by Brookhaven consultant ophthalmologists. The lesions observed were typical of toxoplasmosis and included punctate or smooth-edged, roundish, chorioretinal scars with altered pigmentation (Fig. 1). The retinal findings prompted a serologic survey of the population for antibodies to the parasite. A review of medical records of the examined persons indicated that similar lesions had been documented in earlier years by other ophthalmologists, but the possible association with toxoplasmosis had not been commented on. Included in the survey were all individuals in the exposed and comparison groups who presented for medical examination during the survey, as well as other Marshallese who were offered medical examinations at that time. Four hundred thirty-two serum samples were collected and 457 ophthalmologic examinations were performed. Additional sera were collected in 1982 from examinees who were unavailable in 1981, bringing the total to 517. In 1985 follow-up ophthalmologic examinations were performed on 275 individuals known to be seropositive for toxoplasmosis and negative for retinochoroiditis as a result of the 1981–1982 survey.

Toxoplasma antibody testing using a fluorescence immunoassay was performed in the Parasitology Division, Centers for Disease Control.[10] Results were reported as log titers and analyzed as either mean log titer or as positive/

TABLE 1

Toxoplasma *antibodies in Marshallese*

Group	Number tested	Number positive (%)	Mean log titer* ± SD
By sex:			
Male	235	221 (94.0)	
Female	282	264 (93.6)	
Total	517	485 (93.8)	
By age in 1982:			
10–14	10	8 (80.0)	7.9 ± 2.9
15–19	61	57 (93.4)	9.0 ± 2.2
20–29	141	135 (95.7)	8.1 ± 2.3
30–39	113	104 (92.0)	8.5 ± 2.0
40–49	66	60 (90.9)	8.2 ± 2.3
50–59	63	61 (96.8)	8.6 ± 2.0
>59	63	60 (95.2)	8.5 ± 1.8
By island of residence:			
Ebeye	103	99 (96.1)	
Majuro	62	56 (90.3)	
Rongelap	87	78 (89.7)	
Utirik	172	167 (97.1)	
By radiation exposure group:			
Rongelap	62	51 (82.3)	7.9 ± 2.2
Utirik	98	95 (96.9)	8.6 ± 2.0
Comparison	100	96 (96.0)	8.1 ± 2.0
By island, excluding exposed persons:			
Ebeye	68	66 (97.1)	
Majuro	53	51 (96.2)	
Rongelap	71	67 (94.4)	
Utirik	172	167 (97.1)	
By island, born subsequent to fallout:			
Ebeye	not tested		
Majuro	42	38 (90.5)	
Rongelap	36	34 (94.4)	
Utirik	74	72 (97.3)	

* Mean titer of seropositive persons.

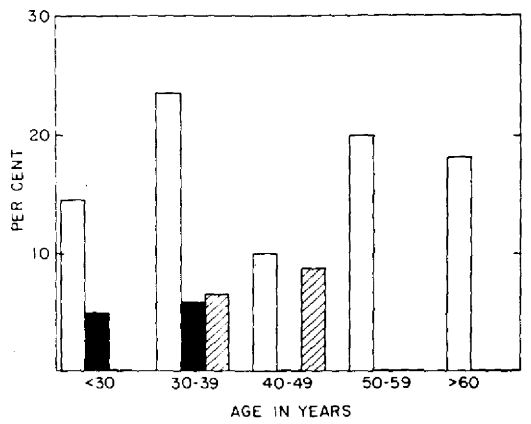

FIGURE 2. Percent of negative tests for antibody to *Toxoplasma gondii* among Marshallese radiation exposure categories: open bars = high exposure group (Rongelap, n = 62); black bars = low exposure group (Utirik, n = 98); hatched bars = unexposed "comparison" population (n = 100).

negative. A "negative" titer was defined as <4 (i.e., negative at serum dilutions <1:16).

The variables analyzed in relation to the *Toxoplasma* titers included sex, age, island of residence at the time serum was drawn, and history of radiation exposure. Ages were normalized to those listed for 1982. Unless specified otherwise, Rongelap refers to the highly exposed group, Utirik to the low exposure group, and "comparison" to the matched control group.

RESULTS

Using the χ^2 test of independence between two or more samples, no significant difference in the prevalence of positive serologic tests for toxoplasmosis was detected among the 517 Marshallese tested when analyzed according to sex (df = 1, χ^2 = 2.78, P = 0.99) or the age groups listed in Table 1 (df = 6, χ^2 = 6.98, P = 0.32). There was a significant variation in distribution of positive tests among the four islands (df = 3, χ^2 = 8.50, P = 0.04) with Rongelap island having the lowest prevalence of antibody (Table 1). Analysis of the three radiation exposure groups revealed that the Rongelap group had a significantly lower prevalence of positive tests than did Utirik (df = 2, χ^2 = 5.95, P = 0.02) or the comparison group (df = 2, χ^2 = 4.69, P = 0.03). The negative tests in the Rongelap group (17.7%) were not clustered around any particular age (Fig. 2). To determine if local environmental factors may have decreased the likelihood of acquiring toxoplasmosis while living on Rongelap island, the prevalence of seropositivity by island was recalculated after excluding the Rongelap exposed group. No significant difference was now detected among the islands (df = 3, χ^2 = 1.18, P = 0.76) (Table 1). Furthermore, negative titers in unexposed current residents of Rongelap (4 of 68 persons) were significantly less common than among the exposed (df = 1, χ^2 = 3.83, P = 0.05). In 152 persons from Rongelap, Utirik, and Majuro who were born subsequent to the fallout (Ebeye was not tested), negative tests were most common on Majuro, although this was not statistically significant (df = 2, χ^2 = 2.51, P = 0.29).

TABLE 2

Prevalence in seropositive Marshallese of chorioretinal scars compatible with toxoplasmosis

By radiation exposure (minimum age, 28 years):	
Rongelap	2/58 (3.4%)
Utirik	4/97 (4.1%)
Comparison	3/95 (3.2%)
Other unexposed persons	5/90 (5.6%)
Total	14/340 (4.1%)
By age (all persons tested):	
10–19	3/65 (4.6%)
20–29	4/135 (3.0%)
30–39	4/104 (3.8%)
40–49	5/60 (8.3%)
50–59	3/61 (4.9%)
>59	0/60 (0.0%)
Total	19/485 (3.9%)

The mean log titers of *Toxoplasma* antibody among seropositive Marshallese, as determined by analysis of variance, did not vary significantly with age (df = 6, F = 1.47, P = 0.19) or history of radiation exposure (df = 2, F = 1.92, P = 0.15) (Table 1). In addition, mean log titers of antibody in the three radiation exposure groups were not significantly different when analyzed by age group at the time of exposure (all P values >0.05).

Twenty-eight persons were found to have retinal lesions compatible with toxoplasmosis, of whom 22 had serum collected for *Toxoplasma* testing. Nineteen of the latter exhibited *Toxoplasma* antibody. The prevalence of chorioretinal scars which were judged as probably or possibly due to toxoplasmosis was similar among seropositive persons in the three radiation exposure groups and a fourth group composed of unexposed persons not included in the comparison population but over 27 years of age (df =

3, $\chi^2 = 0.759$, $P = 0.86$) (Table 2). Persons 27 years of age or younger were excluded from this particular analysis because the youngest exposed individuals were 28 years old in 1982. Since there was no apparent effect of radiation exposure on the prevalence of retinochoroiditis, the combined prevalence for all groups was calculated and found to be 3.9%. The age-specific prevalence of retinochoroiditis in seropositive persons was relatively constant between the ages of 10 and 59 years. Based on the discovery of three new cases of retinochoroiditis in 275 seropositive adults reexamined after 4 years, the incidence was 273 cases/100,000 seropositive adults per year.

DISCUSSION

The high prevalence of antibody to *T. gondii* frequently found among other Pacific populations[5–7] is also present in the Republic of the Marshall Islands. Large local variations in the frequency of positive serologic tests for *T. gondii* were not detected when analyzed according to age, sex, or atoll of residence at the time of serologic testing. Frequent travel by the Marshallese among the atolls may explain the relative homogeneity of the infection. Furthermore, pigs, rats, and fowl are ubiquitous. However, cats, an important source of human infection on some Pacific islands,[11] are currently uncommon on Rongelap and Utirik. Therefore other significant modes of infection may exist, such as ingestion of inadequately cooked cyst-containing meat. Local pork is not eaten frequently, but when it is prepared on festive occasions many persons might be exposed to a single source.

Chorioretinopathy was found in 3.9% of 485 seropositive Marshallese. A prevalence of 11% was found in 192 persons examined on Truk atoll in 1964.[7] However, the Truk lesions were not felt to be typical of toxoplasmosis, despite the presence of *Toxoplasma* dye test antibodies in 80% of the surveyed population, and filarial infection was considered as a possible etiology. Filariasis is not present on the low Marshallese atolls, but retinal lesions are clearly an important health problem. Repeat ophthalmologic examinations performed in 1985 on 275 seropositive persons who had normal eye examinations in 1981 revealed three previously undiagnosed cases of retinochoroiditis. The ages of the individuals were 40, 42, and 53 years. If these were in fact new *Toxoplasma* lesions, the resulting incidence of retinochoroiditis in seropositive persons would be 273 cases/year/100,000 persons. However, the late development of retinochoroiditis in the three individuals is not entirely consistent with the relatively stable age-specific distribution of retinochoroiditis shown in Table 2 nor the current view that ocular toxoplasmosis usually occurs prior to age 40.[12] Of 28 persons with retinal lesions compatible with toxoplasmosis, 5 (18%) had significant visual loss in one or both eyes. With a population of 33,000, a seropositivity prevalence of 93.8% in those 10 years of age or older, a prevalence of retinochoroiditis of 3.9% in seropositive persons, and visual loss occurring in 18% of those with retinochoroiditis, one may estimate that as many as 200 visually impaired persons in the Republic of the Marshall Islands owe their disability to toxoplasmosis. These findings suggest that *Toxoplasma* epidemiology in the Republic of the Marshall Islands differs from that previously reported for other Pacific islands where it was theorized that the ubiquity of early childhood infection made clinically significant toxoplasmosis and fetal infection unlikely.[6] It was cautioned, however, that clinically significant toxoplasmosis might become more common as sanitation practices improved.

Against this background, antibody to *T. gondii* was assessed in a subpopulation of Marshallese accidentally exposed to radioactive fallout in 1954. The finding of significantly fewer positive titers for *Toxoplasma* antibodies among the people of Rongelap who received 110–190 rads of whole-body gamma radiation suggests that the relative infrequency of antibody in this subgroup may be related to their high radiation exposure. However, mean antibody titers in seropositive persons in this group, even when analyzed by age, were similar to those in persons considered to have either a low radiation exposure (11 rads for the Utirik population) or none at all. The prevalence of seronegative individuals was increased in the Rongelap group for all age categories. The prevalence of positive titers in the Rongelap group was significantly lower than that of unexposed adults currently living on Rongelap, a finding which does not support the conclusion that that island has provided less opportunity for acquiring toxoplasmosis than the other islands studied.

Clinically there appears to be no evidence that toxoplasmosis has posed a greater problem for

the Rongelap group: retinochoroiditis has occurred with similar frequency among the different exposure categories (Table 2). Two Rongelap individuals had retinal findings compatible with *Toxoplasma* chorioretinitis but no detectable antibody. Since a combination of retinal and serologic evidence is required for a diagnosis of *Toxoplasma* chorioretinitis,[13] their eye lesions presumably have some other etiology. Severely immunosuppressed persons occasionally develop seronegative toxoplasmosis,[1] but no clinical features suggest severe immunosuppression in the Rongelap group, nor would it be anticipated from the radiation dose they received. There is no evidence for the introduction of bias into the 1981–1982 findings due to earlier mortality in the exposed groups because survival curves since 1954 are virtually identical to that of the comparison group.[9] The proportion surviving in the Rongelap, Utirik, and comparison populations in 1982 was 74%, 70%, and 70%, respectively.

No propensity for any type of infection has been documented as a delayed effect of radiation exposure in Japanese atomic bombing survivors or the exposed Marshallese.[14,15] Recent evaluation of the exposed Marshallese has revealed serum levels of immunoglobulin and skin test reactivity to tuberculin and Candidin to be similar to the comparison population.[16] Nevertheless, seropositivity and antibody titers to each of 10 infectious agents were lower in the Rongelap group than in the comparison population when tested a few years after exposure.[17] In addition, blood lymphocyte concentrations have generally been about 15% lower in the Rongelap group. Impaired lymphocyte responsiveness to PHA, an increased prevalence of hepatitis B surface antigenemia, and perhaps an increase in cirrhosis associated with hepatitis B have been reported in Japanese exposed to > 100 rads.[18–20] It is therefore prudent not to consider the matter of susceptibility as settled, pending further observations with diagnostic techniques unavailable in earlier post-exposure years. With regard to toxoplasmosis, an infection controlled primarily by cellular immune mechanisms, serum levels of antibody during immunosuppression may be relatively unimportant.[21,22] Therefore, if the increased prevalence of seronegativity in the more highly exposed Marshallese reflects defective *T. gondii* antibody induction or production, it may be clinically insignificant. Nevertheless, the number of persons in the high dose group is small. Drawing an analogy with the stochastic nature of neoplastic disease following irradiation, a significant increase in incidence of *T. gondii* reactivation conceivably might be detectable in a larger population.

ACKNOWLEDGMENTS

This investigation was supported by the U.S. Department of Energy under contract DE-AC02-76CH00016.

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